

Congenital Limb Reduction Defects in the Agricultural Setting

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Abstract: To ascertain whether parental involvement in agricultural work and residence in an agricultural setting are associated with the development of congenital limb reduction defects, we carried out a case-control study using California birth records from 1982, 1983, and 1984. Cases with limb reduction defects (N = 237) and randomly selected controls (N = 475) were compared regarding parental occupation and maternal county of residence.

After adjustment for potential confounders in a multivariate analysis, the estimated relative risk (RR) of parenting a child with a limb reduction defect among parents involved in agricultural work was 0.9 (95 per cent confidence limits = 0.4, 1.7). The RR among

mothers who resided in a county of high agricultural productivity as compared with minimal agricultural productivity was 1.7 (95% CL = 1.1, 2.7), while the RR associated with residence in a county with high pesticide use as compared with minimal pesticide use was 1.9 (95% CL = 1.2, 3.1). When we limited the cases to children with limb reduction defects who had at least one additional anomaly (n = 79) and compared them to the control births, the corresponding RRs were 1.6 (95% CL = 0.7, 3.6), for parental involvement in agricultural work, 2.4 (CL = 1.2, 4.7) for county agricultural productivity, and 3.1 (CL = 1.5, 6.5) for county pesticide use. (*Am J Public Health* 1988; 78:654-659.)

Introduction

Thalidomide has been convincingly shown to induce congenital limb reduction defects.¹ In addition, these anomalies have been reported to be associated with the use of birth control pills,² phenytoin,^{3,4} pyridoxine hydrochloride,⁵ haloperidol,⁶ and alcohol.⁷ Previously, we examined birth outcomes in an agricultural community and found the prevalence of congenital limb reduction defects to be increased in the entire community (two- to tenfold higher than available US rates) and also among the progeny of agricultural workers (rate ratio = 2.3).⁸ The findings from that study raised the possibility of an association between the occurrence of limb reduction defects and parental involvement in an agricultural occupation or residence in an agricultural community.

The primary purpose of this investigation is to determine whether parental involvement in an agricultural occupation and maternal residence in an agricultural community are risk factors for the development of congenital limb reduction defects. To address this concern, we conducted a case-control study based on California birth certificates.

Methods

Study Subjects

Study subjects were selected from computerized vital records in the California Department of Health Services including all birth data from January 1, 1982 to December 31, 1984. The study period was chosen so that cases from the study that generated the hypothesis⁸ would be excluded from the current investigation. At the time of case/control definition and selection, information concerning parental occupation was unavailable to the investigators.

Cases included all live offspring born during the study period whose birth certificate recorded one or more shortened or missing limb(s) (ICD codes 755.2-7.55.4). All cases enumerated by this procedure were included in the study. Once identified, these cases numbered 237 and were used to help select subjects for the control group.

The control group was a systematic sample of all live births without any malformations occurring during the study

period. In California, a state file number is assigned sequentially to all birth certificates. We used the state file number to develop a listing for all normal live births. The total number of live births for each year was divided by two times the number of offspring with a limb reduction defect. The quotient of this expression served as the repeating number to systematically select a control group from the listing of normal live births. This selection process resulted in approximately two controls (n = 475) for each case for each of the three years with a control population whose births were distributed throughout the year.

Data Collection

The data for this study were obtained from two sources: a computer-coded birth certificate record and the birth certificate itself. Maternal and paternal occupational data were abstracted from the written birth record by trained nosologists using the same procedures employed by the US Census Bureau for coding occupation and industry.⁹ All relevant data available from the computerized birth record were combined with parental occupational data to form our complete birth record.

The California Department of Health Services has instituted provisions for quality control.¹⁰ The birth certificate information is key-entered onto computer tapes that are then edited for completeness and accuracy. A sample of records is routinely reviewed to identify coding errors. Error rates are regularly reported to be less than 1 per cent.¹⁰ Similarly, the occupational coding procedures and reviews ensure that error rates for these items are less than 5 per cent. During the study period, no modifications in the collecting or coding of birth data were instituted by the California Department of Health Services.

Operational Definitions of Exposure

We chose three complementary measures to estimate the degree of gestational exposure to agricultural chemicals. These measures were based on parental involvement in an agricultural occupation, maternal residence in a county with high per capita agricultural productivity, and maternal residence in a county with high per square mile pesticide use. Given the limitations of our data, we judged these measures to be the most reliable indices for gestational exposure to agricultural chemicals.

For the purpose of this analysis, we grouped the occupational and industrial pairings into agricultural, non-agricultural, and unknown. These pairings were determined without knowledge of birth outcome. In our entire study population,

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homemakers accounted for approximately 50 per cent of our maternal work force, with only six (1.6 per cent) of the working mothers classified as agricultural workers. Therefore, we decided to use a parental category to analyze the effect of agricultural work on the occurrence of limb reduction defects. The parental occupation was recorded as agricultural if either the mother or father was involved in agricultural work. The parental occupation was designated as nonagricultural if neither parent was involved in agricultural work, and was designated as unknown if the occupation of both parents was unknown. In total, 93 per cent of both the cases and controls had a known occupational or industrial designation for at least one of the parents.

The maternal county of residence was used to create two separate measures to approximate gestational exposure to an agricultural setting. The first measure was based on the overall cash value of agricultural productivity by county for 1983 as reported by the California Department of Food and Agriculture.¹¹ This value was expressed as a per capita measure since the relative county productivity is affected by its population. The second measure was based on the use of restricted pesticides by county for 1983.¹² The US Environmental Protection Agency and the California Department of Food and Agriculture designate pesticides as restricted if they are known to be toxic to humans or wildlife or by virtue of their residues pose a risk to the environment. Since we were primarily interested in ambient levels of pesticides available to the gestating population, we reviewed the pesticide use report and eliminated entries of pesticides that were used for industrial and residential pest control. As a means of standardizing for county population and size, we expressed the county pesticide use as a per square mile measure. Using these two measures of gestational exposure to an agricultural setting, the 45 counties in California that were represented by our study population were rank ordered from highly agricultural to non-agricultural. For the purposes of this analysis, the counties that comprised the lowest 35 per cent of our study population were considered minimally exposed. The remaining counties were distributed in the high, medium, and low exposure categories with approximately 20 per cent of the study population in each category. The formulas used to determine relative county exposure and the categorization of counties into minimal, low, medium, and high strata were explicitly performed without knowledge of the county prevalence of limb reduction defects. The Appendix displays the 45 counties that constitute each exposure category for both of the exposure measures.

Data Analysis

The two primary associations studied were those between:

- limb reduction defects and parental involvement in agricultural work; and
- limb reduction defects and maternal residence in an agricultural setting.

Relative risks (RR) were estimated by the odds ratio. The four values (minimal, low, medium, and high) of county agricultural productivity and county pesticide use were used to estimate the RR of limb reduction defects by comparing study subjects in the low, medium, and high exposure categories to those in the minimally exposed group.¹³ For each estimated RR, we calculated the 95 per cent confidence limits.¹⁴ A test for trend, based on the maximum likelihood ratio¹⁵ was used to assess the overall trend of increasing risk of disease with increasing exposure to an agricultural setting.

TABLE 1—Demographic Characteristics, Maternal Medical History, and Birth Characteristics Categorized by Study Group

Demographic Characteristics	Limb Reduction Defects (N = 237)	Control Subjects (N = 475)
Age ≥35 years		
Maternal	11 (4.6)*	23 (4.8)
Paternal	33 (13.9)	78 (16.4)
Birthplace Mexico		
Maternal	27 (11.4)	79 (16.6)
Paternal	28 (11.8)	89 (18.7)
Medical History		
Gravidity	2.0 ± 1.3**	2.2 ± 1.5
Parity	1.8 ± 1.1	2.0 ± 1.2
First Birth	118 (49.8)	202 (42.5)
Prior Intrauterine Termination	42 (17.7)	74 (15.6)
Birth Characteristics		
Months of Prenatal Care	6.4 ± 1.7	6.5 ± 1.7
Birth Season		
December–February	59 (24.9)	119 (25.1)
March–May	46 (19.4)	114 (24.0)
June–August	66 (27.8)	126 (26.5)
September–November	66 (27.8)	116 (24.4)

*N (%).
**mean ± standard deviation.

To assess the extent to which the pattern of malformation affects these associations, we examined these relations for isolated limb reduction defects and limb reduction defects plus at least one additional anomaly. Multiple logistic regression analysis^{13,15} was used to control for the effect of potential confounding variables on the primary associations of interest.

Results

Table 1 presents the demographic and medical history of the cases and controls. The parents of children with limb reduction defects tended to have been born less often in Mexico. Mothers of children with limb reduction defects tended to have a lower gravidity and parity, with the current birth more often being the first birth. The parental age, season of birth, frequency of previous intrauterine terminations (miscarriages and induced abortions), and months of prenatal care during the current pregnancy were similar in the two study groups.

The association between the occurrence of limb reduction defects and our primary exposure variables (parental agricultural work, maternal county agricultural productivity, and maternal county pesticide use) are presented in Tables 2 and 3. Although there does not appear to be an association between limb reduction defects and parental involvement in agricultural work (multivariate RR = 0.9 and 95 per cent confidence limits = 0.4, 1.7), infants with limb reduction defects were more likely to have a mother who resided in a county of high agricultural productivity compared to minimal agricultural productivity (multivariate RR = 1.7 and 95% CL = 1.1, 2.7) or high pesticide use compared to minimal pesticide use (multivariate RR = 1.9 and 95% CL = 1.2, 3.1). Furthermore, a trend of increasing risk is demonstrated from the low to the high category for both measures of environmental exposure (Table 3).

The pattern of malformation was examined to determine if parental involvement in agricultural work or maternal residence in an agricultural setting was more likely to occur

TABLE 2—Relative Risk (RR) of all Limb Reduction Defects (LRD), Isolated LRD and LRD with an Additional Anomaly According to Parental Involvement in Agricultural Work

Comparison	Parental Occupation		RR(95% confidence limits)	
	Agricultural	Non-Agricultural	Crude	Multivariate*
All LRD vs Controls				
No. of cases	13	207	0.8	0.9
No. of controls	33	411	(0.4,1.6)	(0.4,1.7)
Isolated LRD vs Controls				
No. of cases	5	142	0.4	0.5
No. of controls	33	411	(0.1,1.2)	(0.2,1.3)
LRD with another anomaly vs Controls				
No. of cases	8	65	1.5	1.6
No. of controls	33	411	(0.6,3.7)	(0.7,3.6)

*The model includes variables for parental involvement in agricultural work, maternal age, and maternal birthplace (Mexico vs other).

TABLE 3—Relative Risk (RR) of Limb Reduction Defects According to County Agricultural Productivity and County Pesticide Use

Exposure Variable	Relative Exposure				X ² for Trend (P Value)
	Minimal	Low	Medium	High	
County Agricultural Productivity					
No. of cases	74	41	66	56	
No. of controls	190	87	112	83	
Crude RR	1.0	1.2	1.5	1.7	7.52 (0.006)
Multivariate RR* (95% CL)	1.0	1.2	1.5	1.7	
	—	(0.7,1.9)	(1.0,2.2)	(1.1,2.7)	
County Pesticide Use					
No. of cases	70	62	52	53	
No. of controls	180	102	122	68	
Crude RR	1.0	1.6	1.1	2.0	5.46(0.02)
Multivariate RR* (95% CL)	1.0	1.5	1.0	1.9	
	—	(1.0,2.4)	(0.6,1.6)	(1.2,3.1)	

*The model includes indicator variables for low, medium, and high exposure, maternal age, and maternal birthplace (Mexico vs other).

with infants who had isolated limb reduction defects or with infants who had limb reduction defects and at least one additional anomaly. Of 237 infants with limb reduction defects, 158 were noted to only have this single malformation and 79 had this malformation with at least one additional anomaly. When compared with our sample of normal live births, those with limb reduction defects and an additional anomaly were more likely to have parents involved in agricultural work (multivariate RR = 1.6, 95% CL = 0.7, 3.6) (Table 2). Similarly, infants with limb reduction defects and an additional anomaly had a greater risk of having a mother who resided in a county of high agricultural productivity (multivariate RR = 2.4, 95% CL = 1.2, 4.7) (Table 4); or high pesticide use (multivariate RR = 3.1, 95% CL = 1.5, 6.5) (Table 4). Comparing infants having limb reduction defects and an additional anomaly with our sample of normal control births, a trend of increasing risk was noted across the categories from low to high exposure for both agricultural productivity and pesticide use (Table 4). In contrast, when compared to infants with limb reduction defects and an additional anomaly, infants with isolated limb reduction defects were less likely to have a parent involved in agricultural work (multivariate RR = 0.5, 95% CL = 0.2, 1.3) (Table

TABLE 4—Relative Risk (RR) of Isolated Limb Reduction Defects (LRD) and LRD with an Additional Anomaly According to County Agricultural Productivity and County Pesticide Use

Comparison/Exposure Variable	Relative Exposure				X ² For Trend (P Value)
	Minimal	Low	Medium	High	
Isolated LRD vs Controls					
County Agricultural Productivity					
No. of cases	54	27	41	36	
No. of controls	190	87	112	83	
Crude RR	1.0	1.1	1.3	1.5	3.10(0.08)
Multivariate RR* (95% CL)	1.0	1.0	1.3	1.5	
	—	(0.6,1.8)	(0.8,2.0)	(0.9,2.5)	
County Pesticide Use					
No. of cases	52	39	35	32	
No. of controls	180	102	122	68	
Crude RR	1.0	1.3	1.0	1.6	1.70(0.19)
Multivariate RR* (95% CL)	1.0	1.3	0.9	1.6	
	—	(0.8,2.2)	(0.5,1.5)	(0.9,2.8)	
LRD with an additional anomaly vs. Controls					
County Agricultural Productivity					
No. of cases	20	14	25	20	
No. of controls	190	87	112	83	
Crude RR	1.0	1.5	2.1	2.3	7.52(0.006)
Multivariate RR* (95% CL)	1.0	1.5	2.2	2.4	
	—	(0.7,3.2)	(1.1,4.2)	(1.2,4.7)	
County Pesticide Use					
No. of cases	18	23	17	21	
No. of controls	180	102	122	68	
Crude RR	1.0	2.3	1.4	3.1	6.98(0.008)
Multivariate RR* (95% CL)	1.0	2.4	1.4	3.1	
	—	(1.2,4.3)	(0.7,3.0)	(1.5,6.5)	

*The model includes indicator variables for low, medium and high exposure, maternal age, and maternal birthplace (Mexico vs. other).

2) and of having a mother who resided in a county of high agricultural productivity (multivariate RR = 1.5, 95% CL = 0.9, 2.5) or high pesticide use (multivariate RR = 1.6, 95% CL = 0.9, 2.8) (Table 4).

Discussion

Our findings indicate that maternal residence in an agricultural community is a risk factor for the development of congenital limb reduction defects. The apparent teratogenic effect of this environmental exposure is most pronounced among infants with limb reduction defects and at least one additional anomaly.

The smaller association between parental involvement in agricultural work may be an underestimate owing to misclassification of maternal occupation. In our study, 50 per cent of the mothers in both the cases and controls were noted to be homemakers. At least 30 per cent of mothers who are designated as homemakers on the birth certificate have been shown to be gainfully employed during their pregnancy.¹⁶ Moreover, these misclassified homemakers tend to over-represent nonprofessional forms of employment.¹⁶ Since teratogenesis is probably more dependent on maternal gestational exposures, any such underreporting of maternal occupation in our study may have precluded the appropriate comparison (e.g., maternal involvement in agricultural work and the occurrence of limb reduction defects). Unfortunately, given the limitations of our data, we are unable to explore this possibility.

If our findings are valid, at least one of several distinguishing features of the agricultural setting may be responsible for the increased risk of parenting a child with a limb

reduction defect. Although pesticides are the most obvious toxic agent, other environmental exposures that are unique to the agricultural setting include inorganic and organic fertilizers and specific pollens. Pesticide residues have been found in human fetal tissue from women residing in rural agricultural areas,¹⁷ and if administered in sufficiently high doses, three separate classes of commonly used agricultural pesticides (organophosphates, carbamates, and chlorophenoxy herbicides) have been shown to induce skeletal anomalies in laboratory animals.¹⁸⁻²¹ In addition, gestational exposure to pesticides has been associated with the development of other birth defects, including musculoskeletal malformations,²² cleft palate,²³ and coarctation of the aorta.²⁴ Nevertheless, although we used, amount of pesticides by county, as a proxy measure for gestational exposure to an agricultural setting, one should not interpret our positive result to indicate a generic teratogenicity of pesticides. Additional details regarding individual maternal gestational exposures are needed to determine the agent or parental characteristic that is responsible for this association.

Our results indicate a stronger association between the occurrence of limb reduction defects and our exposure variables (parental involvement in agricultural work and maternal residence in an agricultural setting) among infants with additional anomalies compared with infants with only limb reduction defects. Given the clinical manifestation of other environmental teratogens,²⁵ this finding is not unusual and is compatible with a malformation syndrome induced by a specific agricultural exposure.

Since no direct measure of exposure to an agricultural setting was available within our data set, we had to create a measure to approximate this exposure. For this purpose, we chose two separate but related indices of agricultural intensity: county agricultural productivity in dollars, and county pesticide use in pounds. Although these measures of exposure may be helpful in ranking counties based on agricultural intensity, they are inadequate to distinguish individual levels of exposure. This form of misclassification would lead to underestimation of the risk of limb reduction defects associated with exposure to an agricultural setting. Although we attempted to control for confounding by expressing relative risks of limb reduction defects that were corrected for maternal age and maternal origin of birth, other unaccountable factors, such as gestational use of medications, may be responsible for our findings.

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APPENDIX
Measures of Exposure to an Agricultural Setting by Maternal County of Residence*

County Agricultural Productivity				County Pesticide Use			
Minimal	Low	Medium	High	Minimal	Low	Medium	High
Alameda	El Dorado	Butte	Colusa	Del Norte	Riverside	Alameda	Colusa
Contra Costa	Marin	Del Norte	Fresno	El Dorado	San Diego	Butte	Fresno
Los Angeles	Orange	Humbolt	Imperial	Humbolt	San Francisco	Contra Costa	Imperial
Nevada	Sacramento	Lake	Kern	Lake	San Luis Obispo	Madera	Kern
San Francisco	Santa Clara	Mendocino	Kings	Los Angeles	San Mateo	Napa	Kings
		Napa	Madera	Marin	Santa Clara	Orange	Merced
		Placer	Mariposa	Mariposa	Sonoma	Sacramento	Monterey
		San Bernardino	Merced	Mendocino		Santa Barbara	San Joaquin
		San Diego	Modoc	Modoc		Tulare	Santa Cruz
		San Mateo	Mono	Mono			Solano
		Santa Barbara	Monterey	Nevada			Stanislaus
		Santa Cruz	Riverside	Placer			Sutter
		Shasta	San Joaquin	San Bernardino			Ventura
		Solano	San Luis Obispo	Shasta			Yolo
		Sonoma	Stanislaus				Yuba
		Ventura	Sutter				
			Tulare				
			Yolo				
			Yuba				
<i>Study Population</i>							
N(%) 264(37)	128(18)	178(25)	139(20)	250(35)	164(23)	174(25)	121(17)

*Only 45 of California's 58 counties are represented in our study population.

Carnegie Corporation of New York Establishes New Commission of Science, Technology, and Government

Carnegie Corporation of New York has established an new nonpartisan commission to assess the mechanisms by which the federal government and the states incorporate scientific and technological knowledge into policy and administrative decision making. The new Commission on Science, Technology, and Government is co-chaired by Joshua Lederberg, president of The Rockefeller University, and William T. Golden, president of the New York Academy of Sciences.

In addition to eminent scientists, the Commission includes former government officials, who have served at high levels in all branches of government, as well as leaders from nongovernmental sectors.

In making the announcement, David A. Hamburg, the Corporation's president, said, "The main purpose of the Commission is to seek ways in which the branches of government can encourage and use the contributions of the national scientific community. The nation needs more effective mechanisms, both governmental and nongovernmental, for analyzing thoroughly and objectively what science can do for society and how society can make sure that scientific and technological capabilities are humanely used. Although the main focus will be on the federal government, its interactions with state governments and the private sector will also be considered."

The Commission, based in New York City, will organize studies, issue interim reports, and make its final recommendations in about three years, with a two-year follow-up period. The Commission's executive director is David Z. Robinson, a research physicist and former staff member of the US Office of Science and Technology, Executive Office of the President. Most recently he has been executive vice president and treasurer of Carnegie Corporation.