Descriptive Epidemiology of Limb Reduction Deformities in Hawaii, 1986-2000

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Abstract

The relationship between limb reduction deformities and clinical and demographic factors in Hawaii during 1986- 2000 were examined using population-based birth defects program data. The limb defect rate was highest with maternal age less than 20 years, and the defect was more common among males. Among racial/ethnic groups, Pacific Islanders and Filipinos had higher rates than whites and Far East Asians.

Introduction

Limb reduction deformities are easily detectable birth defects with a reported prevalence of 2.0-6.9 per 10,000 births in the United States.[1-4] Various teratogens have been associated with limb reduction deformities, most notably thalidomide but also phenytoin, warfarin, valproic acid, misoprostol, chorionic villus sampling, dilation and curettage, and placental trauma.[5]

As a result of this association between limb reduction deformities and teratogens, a number of population- and hospital-based investigations have been performed in order to delineate the descriptive epidemiology of the birth defect. A large portion (47%-88%) of limb reduction deformities are isolated defects, and chromosomal abnormalities occur in 1%-7% of cases.[1,3,6-13] Limb reduction deformities more frequently affect the upper limbs[1,3,10-12,14] and are unilateral.[3,10,14] Since limb reduction deformities may be identified on prenatal ultrasound, a proportion of cases may be electively terminated.[1,6,9,14,15]

Demographic factors that have been observed by studies to be associated with limb reduction deformities include delivery period,[2,13] maternal age,[3,16] place of residence,[7,8,17,18] plurality,[19] birth weight,[4,8,10,12,14,15,20] and gestational age.[8,12,14] Factors not reported to be associated with limb reduction deformities include race/ethnicity[3,11,14,18] and sex.[3,8,11,13-15,21]

However, population-based epidemiologic data on limb reduction deformities in the United States have been derived from only a few states - California,[18,22] Georgia,[2,18,21,23,24] New York,[3,4] and Texas[25] - with additional hospital-based data from Massachusetts.[1] Moreover, some of the investigations examined only one or several variables in relation to a number of different birth defects, including limb reduction deformities. And the birth defects registries from which some of the data were derived differ in case ascertainment and data sources.[26] In addition, the majority of births in these states are white. For example, among the states in question 64%-85% of the births in 2000 were white while 3%-12% of the births were Asian or Pacific Islander.[27]

The intent of the present investigation is to examine the relationship between limb reduction deformities and various clinical and demographic factors in Hawaii during a recent fifteen-year period. In Hawaii during 2000, the majority (73%) of the births were Asian or Pacific Islander while 23% were white. The epidemiology of limb reduction deformities in Hawaii has not been described in detail using population-based data previously.

Methods

Cases for this investigation were obtained from the Hawaii Birth Defects Program (HBDP), a population-based birth defects registry for the entire state of Hawaii.[26] HBDP inclusion criteria are all live births, fetal deaths, and elective terminations of all gestational ages where delivery occurs in Hawaii and one or more reportable birth defects are diagnosed between conception and one year after delivery. Trained HBDP staff ascertain eligible infants and fetuses and collect demographic and clinical information through review of logs and medical records at all delivery and tertiary care pediatric hospitals, facilities that perform elective terminations secondary to fetal anomaly, cytogenetic laboratories, and genetic counseling offices and all but one of the major prenatal ultrasonography centers in the state. Through this multiple source ascertainment system, few infants and fetuses with diagnosed birth defects are believed to be missed. If an eligible infant or fetus is missed at one ascertainment source it is likely to be identified at another. However, due to the sensitivity associated with elective terminations, it is possible that some elective terminations with birth defects may not be reported in the data sources used by the HBDP. Moreover, it is possible that a prenatal diagnosis of a limb reduction deformity may have been made where no defect actually existed. If the defect was not ruled out after the end of the pregnancy, then the HBDP would include such infants and fetuses as cases when they should not be. The HBDP has no information on the frequency this misdiagnosis occurs but anticipates its impact to be minor and effect mainly elective terminations.

Cases were all infants and fetuses of any pregnancy outcome delivered during 1986-2000 with a diagnosis of limb reduction deformity. Infants and fetuses were excluded if the diagnosis of limb reduction deformity had not been confirmed or if the diagnosis was reported as brachydactyly. Each case was reviewed to determine the type of limb reduction deformity (table 1). Cases were also classified by the level of the defect (upper limb only, lower limb only, both upper and lower limbs), laterality, and whether the defect was isolated or occurred in the presence of other major birth defects.

The total limb reduction deformity rate was calculated. The distribution of all cases by pregnancy outcome, type of deformity, level of deformity, laterality, and presence of other birth defects was determined. The types of chromosomal abnormalities confirmed by cytogenetic analysis and other syndromes identified among the cases was described.

Time trends were investigated by two methods. First, the rate for each year was computed and examined for yearly trends. Several studies have suggested that risk for limb reduction deformities may be reduced with maternal use of multivitamins, and in particular folic acid.[22,24,28,29] The United States Food and Drug Administration had recommended fortification of enriched grain products with folic acid in 1996, with the recommendation becoming mandatory on January 1, 1998.[30] Thus the fifteen-year time period of the study was also divided into 1986-1996 (pre-fortification), 1997-1998 (voluntary fortification), and 1999-2000 (mandatory fortification) and the limb reduction deformity rates between the time periods compared by calculating the rate ratio.

The limb reduction deformity rates were also calculated for maternal age, race/ethnicity, residence at delivery, sex, plurality, and (for live births) birth weight and gestational age. The rates in the various subgroups were compared by computing the rate ratio. Since risk of chromosomal abnormalities have been associated with advanced maternal age, the maternal age analysis was performed for all cases and cases with a known chromosomal abnormality were excluded. The analysis of race/ethnicity was restricted to the four most common racial/ethnic groups - white, Far East Asian (Japanese, Chinese, Korean), Pacific Islander (Hawaiian, Samoan, Guamanian), and Filipino. Investigation of residence at delivery was limited to those cases with a residence in Hawaii and was analyzed by county and whether the residence was in metropolitan Honolulu (zip codes starting with 968) or the rest of Hawaii (zip codes starting with 967). All the variables were not always available for all of the cases, so the sum of the subgroups may not always equal the total number of cases.

Table 1.—Classification of limb reduction deformities

Type of defect	Descrption of defect
amputation/transverse	distal segments of a limb are completely or partially absent with the proximal segments present, e.g., absent hand and fingers
longitudinal	the part of a limb that is parallel to the long axis is completely or partially absent, e.g., absent radius
intercalary	proximal or middle segment of a limb is completely or partially absent with the distal segment existing, e.g., absent upper arm with the forearm and hand present
other	limb reduction deformity not classifiable into the other categories, multiple limb defects that would fit into more than one of the other categories, and split hand and foot

Due to the relatively small number of cases, the various analyses were performed for all cases and not for the individual types of limb reduction deformity.

Denominators were obtained from the Hawaii Department of Health Office of Health Status Monitoring as extracted from birth certificates. Since fetal death certificates and elective termination certificates are considered to be incomplete, information from these were not included in the denominators. Trends were analyzed by the Chi- square tests for trend. Ninety-five percent confidence intervals (95% CI) for rates and rate ratios were calculated by Poisson probability.

Results

There were 125 cases of limb reduction deformities delivered in Hawaii during 1986-2000. There were 281,866 total live births delivered during the same time period, resulting in a rate of 4.4 per 10,000 live births (95% CI 3.7-5.3). The cases consisted of 108 (86.4%) live births, 8 (6.4%) fetal deaths, and 9 (7.2%) elective terminations.

Seventy (56.0%) of the cases were amputation/transverse defects, 34 (27.2%) longitudinal defects, 9 (7.2%) intercalary defects, and 12 (9.6%) other. Limb reduction deformities affected the upper limb alone in 82 (65.6%) cases, lower limb alone in 19 (15.2%), both upper and lower limbs in 21 (16.8%), and the affected limb was unknown in 3 (2.4%) cases. The laterality of the limb reduction deformity was unknown for 13 of the cases. Of those cases with a known laterality, the defects was bilateral for 53 (47.3%) of the cases and unilateral for 59 (52.7%)

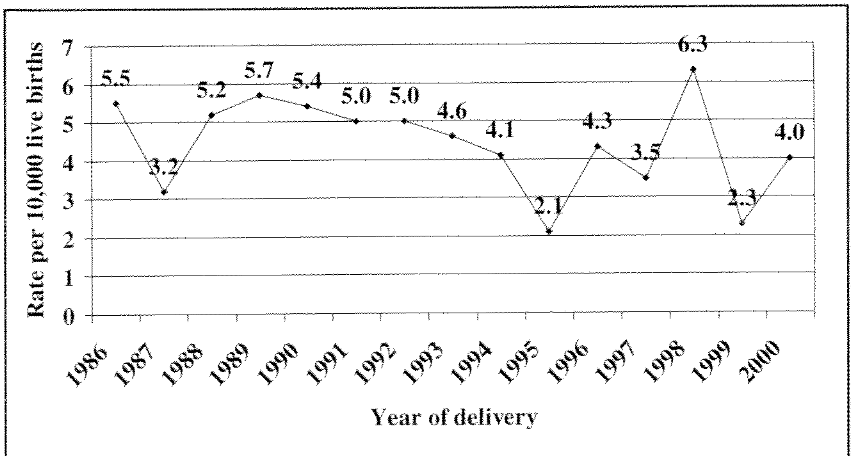

Figure 1. — Rate of limb reduction deformaties by year, Hawaii, 1986-2000

Table 2.—Rate per 10,000 live births of limb reduction deformities by delivery period, maternal age, and maternal race/ethnicity, Hawaii, 1986-2000

Variable	Total	Cases		
	Live births	No.	Rate	Rate ratio
Time period (folic acid fortification status+)				
1986-1996 (before)	212,258	97	4.6	Ref
1997-1998 (transition)	34,887	17	4.9	1.07
1999-2000 (mandatory)	34,721	11	3.2	0.69
Maternal age (years)~				
19	28,492	18	6.3	1.79*
20-24	73,325	35	4.8	1.35
25-29	79,250	28 (1)	3.5	Ref
30-34	63,803	29 (3)	4.5	1.29
35-39	30,472	12 (1)	3.9	1.11
40	6,065	3 (2)	4.9	1.40
Race/Ethnicity				
White	74,236	28	3.8	Ref
Far East Asian	51,264	18	3.5	0.93
Pacific islander	78,396	40	5.1	1.35
Filipino	51,795	26	5.0	1.33

+fortification of flour and other enriched grain products in the United States
~numbers in parentheses are cases with chromosomal abnormalities and are included in the totals
*95% confidence interval does not include 1.00

cases. For one of the unilateral cases, the exact side was not known. For the remaining unilateral cases, the defect was on the left for 31 (53.4%) cases and right for 27 (46.6%) cases.

In 21 (16.8%) of the cases, the limb reduction deformities was isolated. Cytogenetic analysis had been performed for 53 (42.4%) of the cases and chromosomal abnormalities identified in 7 (5.6%) of the cases. All of the chromosomal abnormalities were trisomy 18. Other syndromes were diagnosed in 44 (35.2%) of the cases.

Figure 1 presents the limb reduction deformity rate by year. No significant yearly trend was observed (p=0.262). When the limb reduction deformity rates were evaluated by folic acid fortification period (table 2), the rate was higher during the voluntary fortification period (1997-1998) and lower during the mandatory fortification period (1999-2000) than during the pre-fortification period (1986-1996), although the differences were not statistically significant.

Limb reduction deformity rates by other demographic and clinical factors are shown in tables 2-4. When limb reduction deformities were examined by maternal age, the rate among women less that 20 years was the highest, significantly higher than the rate among women 25-29 years (the reference group). The rate tended to decline with increasing maternal age. However, the trend was not statistically significant for either all cases (p=0.289) or cases excluding those with known chromosomal abnormalities (p=0.059).

Limb reduction deformity rates were higher for Pacific Islanders and Filipinos than for whites and Far East Asians, although the differences were not statistically significant. Rates of the defect did not vary substantially by residence at delivery. Limb reduction deformities were significantly more common among males, which comprised 65.3% of the cases of known sex. Rates of limb reduction deformities were significantly higher among the lower gestational age and birth weight groups. Although limb reduction deformities were twice as common among multiple births than among singletons, the difference was not statistically significant.

Discussion

This investigation examined the relationship between limb reduction deformities and various clinical and demographic factors in Hawaii during 1986-2000. Although other population- and hospital-based investigations of limb reduction deformities in the United States have been performed before, some of the studies focused on one or several factors in relation to a number of different birth defects, including limb reduction deformities. Moreover, the data for these studies were derived from predominantly white populations whereas the population of Hawaii is predominantly Asian or Pacific Islander.[27]

The main weakness of this investigation is the small number of cases, particularly when divided among various subgroups. This limited the statistical significance of the analyses, although some statistically significant differences were observed. Moreover, this study provides data that can be used with other data in the literature for meta-analyses.

The rate of limb reduction deformity in Hawaii (4.4 per 10,000 live births) was similar to that reported in New York (4.5) in one study but higher than that in New York in another (2.0) and lower than the rates observed in Massachusetts (6.9) and Georgia (5.3).[1-4] Limb reduction deformity rates have been previously noted to vary between states [18] and between countries.[7,8,17] Thus deviation between the rates observed in the current study and other states might be expected. Differences in rates may reflect differences in case ascertainment[26] or differences in population composition, particularly if the populations differ in a factor associated with limb reduction deformity risk.

The majority of limb reduction deformities were identified among live births, with 6% found among fetal deaths and 7% among elective terminations. This distribution is consistent with the literature, which reported 0%-16% of limb reduction deformities among fetal deaths and 3%-25% among elective terminations.[1,6,7,9,14,15,20]

The most common of the three main types of limb reduction deformity was amputation/transverse defects, followed by longitudinal defects, with intercalary defects being least common. Other studies have reported similar findings, with amputation/transverse defects accounting for 28%-72% of limb reduction deformities, longitudinal defects for 17%-47%, and intercalary defects for 1%-10%.[1,3,7-10,14]

Limb reduction deformities were observed to affect the upper limbs more frequently, a pattern noted in the literature.[1,3,10-12,14] This differential effect could be due to differences between upper and lower limbs in timing of development or susceptibility to teratogens. The limb defects were unilateral only slightly more often than bilateral, and 53% of the unilateral defects occurred on the left side. Other investigations had noted limb reduction deformities to be unilateral 72%-80% of the time,[3,10,14] and some studies reported unilateral defects to occur more often on the right [11,23] while another found the defects more common on the left.[14]

Only a fraction (17%) of the limb reduction deformities were isolated defects, contrasting with the much higher isolated rate of 47%-88% found by other investigations.[1,6,7,8,10-14] Potential explanations for this discrepancy include more thorough identification of additional birth defects by the current study or differences in what would be considered additional major birth defects. The former explanation is supported by the observation of a general decline in the proportion of limb reduction deformities considered to be iso-

Table 3.—Rate per 10,000 live births of limb reduction deformities by delivery residence and infant/fetus sex, Hawaii, 1986-2000

Variable	Total	Cases		
	Live births	No.	Rate	Rate ratio
Delivery residence				
City & County of Honolulu	223,318	95	4.3	Ref
Hawaii County	31,856	12	3.8	0.89
Maui County	27,548	10	3.6	0.85
Kauai County	13,562	6	4.4	1.04
Metropolitan Honolulu	84,949	37	4.4	0.99
Rest of Hawaii	195,843	86	4.4	Ref
Sex				
Male	144,835	81	5.6	Ref
Female	136,597	43	3.1	0.56*

*95% confidence interval does not include 1.00

Table 4.—Rate per 10,000 live births of limb reduction deformities by plurality, birth weight, and gestational age, Hawaii, 1986-2000

Variable	Total	Cases		
	Live births	No.	Rate	Rate ratio
Plurality				
Singleton	274,512	120	4.4	Ref
Multiple birth	5,723	5	8.7	2.00
Birth weight (live births)				
2,500 grams	19,752	43	21.8	8.94*
2,500 grams	258,730	63	2.4	Ref
Gestational age (live births)				
38 weeks	43,151	43	10.0	3.44*
38 weeks	224,321	65	2.9	Ref

*95% confidence interval does not include 1.00

lated over time in the literature. Of the studies published during 1982-1990, the average proportion of limb reduction deformities classified as isolated was 73%, while during 1991-2001 the analogous proportion was 55%. The 6% chromosomal abnormality rate among limb reduction deformity cases was consistent with the 1%-7% range reported by other studies.[1,3,6,8,11,14]

No clear yearly trend was observed in limb reduction deformity rates in Hawaii during 1986-2000. Although one investigation had reported a significant increase of the limb defects in 1964-1977 [13] and another a decrease in 1968-1993,[2] the majority of studies have reported no yearly trend for limb reduction deformities in the 1960's to the 1990's.[7,11,15,20]

The limb reduction deformity rate was lower during 1999-2000, the period of mandatory folic acid fortification of enriched cereals, than during 1986-1996, the period prior to folic acid fortification. However, the difference was not statistically significant, and the limb reduction deformity rate during 1997-1998, the period of voluntary folic acid fortification, was higher than the other two time periods. Moreover, the limb reduction deformity rates in 1999 and 2000 were higher than the rates in several years during 1986-1996. This would tend to suggest that folic acid fortification has not resulted in a significant decrease in limb reduction deformities in Hawaii. Data collection over more years of mandatory folic acid fortification will be useful for confirmation of this observation.

The highest limb reduction deformity rates were identified among the lowest maternal age group, and the rates tended to decline with increasing maternal age. This is contrary to the literature, which has reported increased risk of the limb defects with advanced maternal age,[16] lower rates among the youngest and oldest maternal age groups,[3] or no association with maternal age.[4,7,8,12] The relationship between maternal age and limb reduction deformity risk observed in the present investigation could be due to differences in exposure or susceptibility to teratogens with maternal age.

Limb reduction deformity rates were lower among whites and Far East Asians and higher among Pacific Islanders and Filipinos, although the differences were not statistically significant. The differences in rates between the racial/ethnic groups could be partially due to differences in maternal age distribution. The proportion of cases with maternal age less than 30 years was 53.6% (15/28) for whites, 38.9% (7/18) for Far East Asians, 80.0% (32/40) for Pacific Islanders, and 69.2% (18/26) for Filipinos. Racial/ethnic differences in limb reduction deformity rates could also be due to differences in environmental exposures or genetic factors between the groups. Rates for comparable racial/ethnic groups are not readily available from the literature; however, race/ethnicity has not been reported by other studies to be substantially related to limb reduction deformity risk.[3,11,14,18]

Limb reduction deformities were significantly more common among males than females. Although other studies have also reported a higher proportion of the defect among males, the proportion of limb reduction deformities represented by males (53%-57%) was lower than the current study (65%), and the sex differences were not statistically significant.[3,8,11,14,15,20,21] It is unclear why the sex ratio in the present investigation would demonstrate even greater deviation from expected. Some potential explanations offered for sex differences in birth defects include differences in development and differentiation of the urogenital system, influence of sex hormones, fetal rates of growth and maturation, and susceptibility to teratogens.[21]

Plurality did not substantially influence limb reduction deformity rates while rates for the defects were significantly higher with lower birth weight and gestational age. These findings are consistent with the literature with respect to multiple births,[14,15,31] birth weight,[4,8,10,12,14,15,20] and gestational age.[8,12,14]

In conclusion, the proportion of limb reduction deformities that were isolated was lower than that reported by other studies. Although several investigations had reported that folic acid reduced risk of limb reduction deformities, the limb reduction deformity rate was not substantially lower in Hawaii after folic acid fortification of various food products. The limb reduction deformity rate was highest with maternal age less than 20 years, and the defect was more common among males. Among racial/ethnic groups, Pacific Islanders and Filipinos had higher rates than whites and Far East Asians.

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