

# Maternal Factors, Medications, and Drug Exposure in Congenital Limb Reduction Defects

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As part of an ongoing study on all limb reduction defects occurring among 1,213,913 consecutive live births in the province of British Columbia, Canada, during 1952-1984, cases with documented maternal drug exposure and chronic maternal diseases were analyzed separately. This population-based study was made possible through the existence of an ongoing Health Surveillance Registry, which documents all infants born with congenital, genetic, or chronically handicapping conditions in the province of British Columbia. Strict rules of confidentiality are obeyed. For this part of the analysis of limb reduction defects, cases with documented maternal illness, drug abuse, and exposure to environmental hazards early in pregnancy were analyzed as a separate group to identify specific, recurring patterns of anomalies. A total of 51 cases with possibly related maternal factors were identified. Among them were five cases with maternal epilepsy, four cases with documented maternal diabetes, and three cases with uterine anomalies. Three infants, all born in 1962, had documented thalidomide exposure. It is rarely possible to identify particular teratogenic factors or specific maternal factors as etiologically related to the pattern of limb reduction defects or a spectrum of congenital malformations. Exposure to environmental factors during pregnancy is not reliably registered and can thus only occasionally be ascertained in retrospective studies. This means that very large numbers of cases and cross-referencing to other family members are required to assess whether a potential teratogen is related to limb defects or not.

## Introduction

Limb reduction defects are regarded as indicators for teratogens and are easily recognizable and not often missed. A number of teratogens etiologically related to defects of limb development have been identified to date. Not all of these teratogens cause a highly specific pattern of limb reduction defects. The most widely known teratogen causing limb reduction defects is certainly thalidomide (1), but other limb reduction defect patterns have been associated with prenatal exposure to hydantoin (2), ethanol (3), cocaine (4), and possibly mechanical vascular disruption by early chronic villus sampling (5).

If a chemical is involved, the resulting limb reduction defects may be very specific. Thus, thalidomide would cause intercalary transverse defects ("phocomelia"), while hydantoin causes defects of the terminal phalanges. With regard to ethanol, the amount consumed and the individual biological background are also additional factors in the expression of defects. The ethanol related spectrum of

limb reduction anomalies ranges from very severe forms such as amelia, ectrodactyly, and unilateral terminal transverse defects of the hand to hypoplastic end phalanges or small fingernails (3).

## Material and Methods

The data are derived from a large study on limb reduction defects occurring in 1,213,913 consecutive live births in the province of British Columbia during a 30-year period from 1952 to 1984 (6). The study was made possible through the existence of a Health Surveillance Registry (Registry) that collects information on all infants born with malformations, genetic diseases, or individuals developing chronically handicapping conditions. The Registry receives information from over 60 different sources, the most important ones for the present study being the Physicians Notice of Birth and Hospital separation sheets. Within the Registry cases are coded according to the ninth revision of the International Classification of Diseases code of the World Health Organization. Incoming cases are cross-referenced to any other family members already registered. Therefore, if a mother of an infant born with a malformation is registered to have a congenital malformation or chronically handicapping condition, this

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information is identified. Details of the organization of the Registry have been reported previously (6,7).

Incidence rates for various categories of limb reduction defects, and analysis of upper and lower limb defects aimed at identifying specific patterns of congenital malformations have been published previously (6,8). However, the aspect of possible teratogenic exposures and their role in limb defect causation required a more detailed evaluation. Because of the rules of strict confidentiality at the Registry, it is not possible to personally examine patients. Therefore, those cases with a documented chronic maternal illness, and documented drug exposure or acute maternal illness during pregnancy were extracted from the complete body of data. These cases were evaluated for possible common patterns of anomalies, both of the limbs and other organ systems, seen after exposure to particular maternal factors. It is recognized that more mothers of infants with limb defects in the study may also have had similar exposure or maternal factors present, but this fact is not recorded. Even though ascertainment of these factors is therefore incomplete, there is no reason to expect this would necessarily invalidate any pattern observed.

## Results

The results are summarized in Tables 1–5. Nine cases with prenatal ethanol exposure were described previously and are thus not included (3). There remained a total of 51 cases, which were divided into four subgroups based on similar etiological factors: *a)* chronic maternal diseases, *b)* maternal congenital anomalies, *c)* acute maternal infections in pregnancy, *d)* exposure to medications, X-rays, environmental hazards, or drugs in pregnancy.

## Chronic Maternal Diseases

Maternal diabetes was registered in four cases (Table 1); three males and one female. Three of these infants had intercalary defects of the femur or tibiae. One had additional anomalies of the vertebrae, a pattern that is well recognized as occurring in conjunction with maternal diabetes mellitus and described as caudal regression or unusual-facies-femoral hypoplasia syndrome (9). In one case, defects of the toes and a VSD were found in addition.

Maternal epilepsy was registered in five cases (Table 2), with phenobarbital or Dilantin being specifically mentioned as the medication taken for this condition in three cases. In the remaining cases, no information about the particular medication could be obtained from the Registry. Limb reduction defects in this group were fairly homogeneous, with four out of the five patients presenting with reduction defects of the distal phalanges, either on the left side or bilateral. One infant was also noted to have epilepsy. In two cases other features of the fetal-hydantoin syndrome were specifically mentioned, but because of Registry policy it was not possible to go back to the other individual cases and examine them for particular features of the fetal-hydantoin syndrome. Other maternal chronic diseases included one case each of arthritis, asthma, lupus erythematosus, coeliac disease, and elevated testosterone levels (Table 3).

## Maternal Congenital Anomalies

Congenital defects were registered in mothers of 10 infants (Table 4). Four of them had skeletal anomalies, which may thus be genetic limb defects with variable

Table 1. Cases with limb reduction defects and maternal diabetes.

Case	Sex	Year of birth	Limb defect	Other anomalies
1	M	1969	Intercalary, femora	Hemivertebrae L4, club feet
2	M	1980	T1, tibia, fibula, left	Inguinal herniae, right, left, caudal regression
3	F	1981	T1, phalanges, left, upper	Low-set ears, microtia, left, VSD, prematurity
4	M	1983	Intercalary, femur, left	Cryptorchidism, dimple over right knee, prematurity

Table 2. Cases with limb reduction defects where the mother had epilepsy.

Case	Sex	Year of birth	Maternal medication	Limb defect	Other anomalies
1	F	1952	None	Tt, hand, left	
2	F	1953	None	T1, thumb, left, distal	Deafness, short stature
3	F	1957	None	T1, phalanges IV, V, bilateral, distal	Hypertelorism, epilepsy
4	M	1982	Phenobarbital, Tegretal, Dilantin	T1, phalange V, left, distal	Broad nose
5	M	1983	Phenobarbital, Dilantin	Tt, phalange, distal, bilateral	

Table 3. Chronic maternal diseases and limb reduction defects.

Case	Sex	Year of birth	Maternal disease	Limb defect	Other anomalies
1	M	1971	Asthma	T1, phalanges I–IV, left	
2	M	1974	Lupus erythematosus	It, femur, right	Brother: CHD
3	M	1979	Arthritis	T1, phalanges II–V, right, left	
4	F	1983	Coeliac disease	Tt, hand, right	Cousin: Tt, radius, right
5	F	1983	Elevated testosterone levels	T1, phalanges I–IV, right	Prematurity 46, XX, dysmorphic face, seizures, hemangioma on chest, pulmonary stenosis, clitoromegaly

**Table 4. Cases with limb defects and maternal congenital anomalies.**

Case	Sex	Year of birth	Maternal anomalies	Limb defects	Other anomalies
1	F	1955	Tl, toe V, right, left	Tl, toes, V, left	Brother: short fingers; maternal grandmother: syndactyly
2	F	1973	Amniotic bands	Tt, hand, right, left	Asymmetric face mishapen ears, encephalocele, esophageal atresia, constriction bands
3	F	1980	II, thumbs, bilateral cleft palate, syndactyly II/III toes	Tl, phalange, II, right	
4	M	1983	Congenital deformity, right arm	Tl, phalange, II, right	
5	M	1981	Cleft palate	It, radius, left syndactyly	Hip dysplasia, prematurity
6	F	1976	ASD	Tt, femur, right	Esotropia, bilateral, prematurity
7	M	1976	Aortic valve defect	Tl, radius, left	Anencephaly, VSD cleft palate, spina bifida, hypospadias, twin (twin brother healthy)
8	M	1977	Uterus bicornis	Tl, phalanges, II-V, left	
9	F	1983	Uterus bicornis	It, radius, left	Megacephaly, seizures
10	F	1983	Duplication of uterus and cervix single kidney	Tl, ulna, right syndactyly, II/II	

Abbreviations: T, terminal; l, longitudinal; t, transverse; ASD, atrio-septal defect; VSD, ventriculo-septal defect; I, intercalary.

**Table 5. Acute infections during pregnancy and limb reduction defects.**

Case	Sex	Year of birth	Maternal illness	Limb defect	Other anomalies
1	F	1953	Rubella	Tl, thumb, right	
2	F	1965	Rubella	Tl, phal, right It, leg	
3	M	1970	Rubella	Tl, tibia, left	CHD, abnormal ears, cryptorchidism
4	F	1972	Rubella	Tt, toes, right, left	Father, grandfather: deformed toes
5	F	1967	Red measles	Tt, hand, right	
6	F	1970	Varicella	Tt, tibia, fibula	
7	M	1971	Viral infection	Tt, radius, right	Sister: deafness
8	F	1977	Viral infection	Tt, hand, right	
9	M	1978	Viral infection	Tl, phalanges II-IV, right Syndactyly toes IV/V, right, left	
10	M	1979	Viral infection	Tt, hand, left	
11	M	1980	Viral infection	Tt, hand, left	

Abbreviations: T, terminal; l, longitudinal; t, transverse; I, intercalary; CHD, congenital heart defect.

**Table 6. Cases with documented thalidomide exposure.**

Case	Sex	Year of birth	Other drugs	Limb defects	Other anomalies
1	F	1962	—	It, humeri, right, left	Cleft palate, strabismus
2	F	1962	—	Tl, phalanges II-V, left It, humeri, radii, ulnae, right, left	Nevus, flammeus, CHD
3	F	1962	alcohol	It, humeri, radii, ulnae, femora, tibiae, fibulae	Mental retardation, VSD, deafness, nevus flameus, ring around right lower leg

Abbreviations: T, terminal; l, longitudinal; t, transverse; I, intercalary; CHD, congenital heart defect; VSD, ventriculo-septal defect.

expression. However, without personal investigation or access to detailed maternal records, this cannot be decided with certainty. In three cases, maternal uterine anomalies are mentioned. These again could be examples of a specific syndrome with hand and uterus anomalies with variable expression in different generations, such as the ulnar-mammary syndrome (10); in one further case cleft palate in the mother was a feature, in two cases the mother had a congenital heart defect.

**Acute Maternal Infections during Pregnancy**

In 11 cases acute maternal infections during pregnancy were registered (Table 5). This included three cases of

rubella infection and one case with contact to rubella, one case with red measles and one with varicella, and also three cases of a severe viral infection, but further details of the virus in question were not available.

**Exposure to Medications, X-Rays, Environmental Hazards, and Drugs**

Thalidomide was noted in only three cases (Table 6) in this study (6). One of the cases also had prenatal alcohol exposure. The three cases display the well-established pattern of anomalies caused by thalidomide, affecting the skeletal system and causing cardiovascular and functional anomalies (1). It is of interest that the case with alcohol exposure also had mental retardation.

Table 7. Maternal exposures in pregnancy and limb reduction defects.

Case	Sex	Year of birth	Medication/exposure	Limb defect	Remarks
1	M	1969	Marijuana	Tl, phalange, II, right syndactyly IV/V, right	
2	F	1972	Marijuana	It, radius, right It, tibiae, right, left syndactyly I/II, IV/V, right	
3	M	1979	Marijuana	Tl, phalange, II, right syndactyly toes, III/IV	Microcephaly, growth retardation, peculiar face, mental retardation
4	M	1972	Diet pills	Tt, hand, right	
5	F	1977	Diet pills	Tt, hand, right	
6	F	1972	INH from 6 weeks gestation	Tl, thumb, left	46,XX, microphthalmia, small jaw, cleft palate, bulbous nose, neonatal death, duodenal atresia
7	M	1970	Hormonal injections	Tt, hand, right	Hip dislocation hemangioma; sister: duplication of vagina
8	F	1978	Fertility drugs, diazepam	Tl, phalanges IV/V, right	Hip dysplasia
9	F	1970	Gravol Aspirin	Tl, phalanges, II-V, right Tl, toes II-V, right	Bifid uvula
10	F	1971	Skemetil	Tt, hand, right	
11	M	1973	Bonamin	Tl, phalanges, II-IV, left syndactyly IV/V, left	
12	M	1982	Medication for schizophrenia	Tl, phalange V, right	
13	F	1984	Cocaine, alcohol	Tt, hand, right	Ear dysplasia

Abbreviations: T, terminal; l, longitudinal; t, transverse; I, intercalary.

Marijuana was documented as a drug taken in pregnancy in three cases (Table 7). Cocaine was documented in one case, which was described in detail previously (3). There was a single case in which maternal X-ray exposure was documented. In this case a terminal transverse defect of the phalanges of the left hand was found.

Excluded from the analysis was one case with a chromosomal anomaly (ring chromosome 13) and one case with Poland anomaly, in which iron was taken as the only drug during pregnancy and any relationship to the limb defects is very unlikely. Both cases were described previously (6,8).

## Discussion

An analysis of maternal factors with a potential teratogenic effect was undertaken to evaluate if any specific recurring pattern could be recognized.

It is well established that children born to mothers with diabetes mellitus have a two to four times increased risk for congenital malformations. This includes cardiovascular, genitourinary, and central nervous system anomalies; branchial arch malformations have also been described (11). The caudal regression anomaly or femoral hypoplasia-unusual-facies syndrome has been recognized as a developmental field defect occurring frequently in infants of diabetic mothers (12,13). The spectrum of anomalies described in the literature is strikingly compatible in three of the four cases where the mother was identified as diabetic (Table 1). The teratogenic mechanism is not yet well understood, but hyperglycemia appears to have a greater impact in the pathogenesis of defects related to maternal diabetes (14).

Among children of mothers treated with hydantoin (Dilantin), the risk of showing either the full hydantoin

syndrome is 10% and for some signs of the spectrum of anomalies is an additional 33%. As demonstrated in observations of discordant twins, the genetic background is important for the expression of the syndrome features (15). In our study, it is unclear in three of the five cases which particular medication was taken for epilepsy. However, in two cases hydantoin in combination with other drugs was documented and the reduction defects seen are congruent with those described in the literature.

The exposure to chronic maternal disease in our study is very heterogeneous. For maternal arthritis, coeliac disease, and lupus erythematosus circulating antibodies, causing placental thrombosis, have been discussed as possible teratogens (16). A vascular disruption at various times in development is a likely explanation for the majority of cases with chronic maternal disease in our study (17). Maternal cardiovascular anomalies were documented in two cases, one of them showing a very severe pattern of associated anomalies (Table 4). This case is a product of a twin pregnancy, which by itself could contribute to numerous congenital malformations. The causative factor for the observed pattern of fetal anomalies remains unclear.

In eight cases, other maternal congenital anomalies were registered. Four mothers had a skeletal defect, which was similar in the offspring and might very well demonstrate variable expression of a genetic disorder. Of particular interest among these cases is the occurrence of amniotic band sequence anomalies in a mother and her offspring. The infant had in addition a spectrum of anomalies, some of them that were not due to amniotic bands. Similar observations had been reported by Hunter and Carpenter (18). The hypothesis was put forward that this might be due to a familial inherent vascular instability, leading to recurrence of amniotic band sequence.

Mothers of three cases had uterine anomalies. Uterine anomalies have been suggested as a mechanical factor leading to limb anomalies through early *in utero* compression (19). In view of the variable expression in the autosomal dominantly inherited ulnar-mammary syndrome, at least one case described by Graham and co-workers (19) with ulnar-ray reduction is very suggestive for this diagnosis. In two cases from our study, the offspring had ulnar defects, suggesting the ulnar-mammary syndrome as a likely diagnosis (10). Because personal physical examination was not possible, we cannot confirm this.

In the group of acute maternal infections, there were four cases with prenatal rubella exposure, displaying different limb reduction defects. Defects known to be present in the majority of cases with congenital rubella are not documented in the cases from our study, with one exception (congenital heart defect). The only limb defects described in cases with congenital rubella are osteolytic lesions (20). In our study these were not identified. It is not possible to specify the relationship between the observed limb reduction defects in this study and the prenatal viral infection. Among the pathogenetic mechanisms in congenital rubella, inhibition of cell replication has been suggested. Marked slowing of cell doubling time could result, among other anomalies, in reduction defects of the limbs (21).

In fetal varicella (Table 5) limb reduction defects are part of the spectrum of congenital anomalies described in the literature and are frequently associated with cicatricial lesions of the overlying skin (22). In the cases with unspecified viral infections, terminal transverse defects at the metacarpophalangeal level in the majority of cases suggests a vascular disruption (17) and thus are a fairly nonspecific effects of a viral agent.

Thalidomide exposure was documented in three cases in this study. The drug was on the market in Canada for only 11 months during 1962 (23). The pattern of anomalies found in this study is congruent with the expected pattern characteristic for this teratogen (1). At least 25 different hypotheses have been suggested to explain the teratogenic mechanism of this chemical, none of them elucidating the mechanism of action satisfactorily (24).

Marijuana is widely used, so the three cases present here represent a minimal estimate of probable exposed cases. In extended studies among marijuana users, no significant increase in minor or major anomalies has been identified (25), although sporadic case reports of congenital anomalies have been reported (26). In studies on rats, limb reduction defects as well as other congenital anomalies were found (27). The three cases of reduction defects from our study could be a chance occurrence. However, two of them have a strikingly similar pattern of anomalies, namely, reduction defects of the second ray, which is a very unusual anomaly. The incidence for middle-ray defects in the general population in our study was 0.609 in 10,000 live births, and a defect restricted to the second ray is even just a small proportion of this rare event (8).

In the group with miscellaneous drugs and unspecified viral infections (Tables 5 and 7), defects of the distal limb are far more frequent (19/23, 78%) than defects of the

proximal parts of the limbs the limbs (4/23, 17%, mean = 17.04;  $p < 0.001$ ). This is not significantly different from the incidence of distal defects occurring among live births in general, where distal defects occurred in 76% of cases and proximal defects in 24% of cases (6). A high incidence of distal limb defects was also found in studies of mammals (28). An unspecific effect of teratogenic agents interfering with the sensitive time in limb development either as a vascular disruption or inhibition of cell growth has been postulated.

Other studies looking systematically for maternal factors in cases with limb reduction defects have used different classification systems for the limb defects and examined a different spectrum of maternal factors. They are therefore difficult to compare. However, Polednak and co-workers (29) also found diabetes mellitus being associated with "hypoplasia of the lower extremities," apparently involving the long bones, in three out of five cases. Aro (30), in a study of 453 cases with limb reduction defects in Finland, found influenza and rheumatoid arthritis associated with reduction defects of the limbs.

The significance of an association between maternal factors and limb reduction defects is difficult to assess in retrospective studies. In general, a mother of a malformed child will more likely try to find an external cause for the birth anomaly and may thus more actively remember any unusual circumstances during the pregnancy. The figures derived from such studies may therefore be biased. However, because of the paucity of human data, it is worth assessing available databases for any patterns of malformation that appear to be associated with given exposures. Prospective approaches would then be required to confirm any hypothesis regarding causation. In some subgroups from this study (mothers with diabetes, epilepsy, and chronic maternal diseases) the limb reduction defects resembled the pattern that is established in the literature. Even though the numbers are small, databases on limb reduction defects in humans are not common, and it is worth describing and analyzing these so that, together with other studies, insight may be gained.

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