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A prospective study of some aetiological factors in limb reduction defects in Sweden

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ABSTRACT Two groups of infants with limb reduction defects were studied: all such infants born in Sweden 1983–1986, and infants with severe reduction deformities born in 1973–1981. Data on the use of oral contraceptives, intrauterine devices, and drugs, and on maternal smoking were retrieved from information collected in early pregnancy as a part of routine maternity health service records. It was not possible to substantiate the association, described repeatedly in the literature, between limb reduction defects and the use of oral contraceptives just before or in early pregnancy. Various explanations for this discrepancy are discussed. An association with maternal diabetes was seen but not with drugs used for thyroid disease. A weak and statistically non-significant association with maternal smoking was found for severe limb reduction defects.

Limb reduction defects are present in about 7 per 10 000 newborn infants; the majority are made up of transverse reduction defects, and especially loss or hypoplasia of digits.[1] A number of epidemiological studies have been made concerning the aetiology of these defects.[2–10]

Many different exposures and risk factors have been studied. The most consistent finding concerns the use of oral contraceptives. Janerich *et al*[2] found six break-through pregnancies (Pill failures) among their cases and only one among equally many controls. Twelve index case women and only three controls became pregnant within one month of stopping oral contraceptives. In the Hungarian study,[5] oral contraceptives had been used in early pregnancy in 14 cases and nine controls; the use of oral contraceptives the month before conception or during early pregnancy was significantly more common among mothers of infants with limb reduction defects than among control mothers: the risk ratio was 1·6 with 95% confidence interval (CI) of 1·0–2·2. Kricker *et al*[9] found a still stronger effect: 18 cases (12%) but only one control (0·4%) had used oral contraceptives in early pregnancy (exact risk ratio 30·2, 95% CI 5·3–520). These authors did not find an increased risk when the woman had stopped oral contraceptives within one or two months before conception (15 *v* 28; 25 *v* 48). In all three studies, the strongest link between oral contraceptive use and limb reduction defects was seen for transverse reductions. In the recent British drug prescription study,[10] a non-significantly increased odds ratio (1·9, 95% CI 0·8–4·6) was found for oral contraceptives taken three months before the last menstrual period. Four pairs were discordant for exposure during early pregnancy: in all four, the case was exposed.

Other studies (mainly limited prospective ones) have not been able to substantiate the finding but they had a low power. Smith *et al*[4] found no association between the use of oral contraceptives and limb reduction defects in a case-control study, but it is not clear whether exposure information refers to the time of conception or not.

Among other risk factors which have been observed are salicylate use (but mainly after the formative period of limb reduction defects)[5] and thyroid drugs.[3] Czeizel *et al*[5] found mothers of six limb reduction cases but no controls to have used ovulation stimulating drugs, but the occurrance of delayed conceptions (>12 months) in planned pregnancies was not much more frequent among cases (9·5%) than controls (8·0%). Threatened abortion has been identified as a risk factor by some[3 4 7] but not by other studies.[5] Diabetes was suggested as a risk factor in one study[3] but not in another.[5] The presence of an intrauterine device (IUD) has also been suggested, but this has not been verified.[5 9 11]

Because of the rarity of oral contraceptive exposure in early pregnancy and the rarity of limb reduction defects, a classical prospective study will not be informative.[9] However, in Sweden this and similar problems can be studied using information which is collected on all births in early pregnancy. This paper presents such a study on limb reduction defects,

concentrating on the following possible aetiological factors: use of oral contraceptives, IUD, maternal smoking, diabetes, and drugs.

Methods

Since 1973 there has been a Medical Birth Registry in Sweden with medical information on all deliveries. A standardised record form is used in the whole country at maternity health centres (practically every pregnant woman attends such a centre), delivery units (practically all births occur in hospitals), and at the examination of the newborn infant (practically all infants are examined after birth by a qualified paediatrician). Copies of these forms are sent to the National Board of Health and Social Welfare where they are computerised. The records contain information on the pregnancy and delivery and diagnoses given to the infant, including malformation diagnoses. The diagnoses are given as ICD8 codes and are therefore relatively crude.

In 1982, a change in the report form was made. Among other things, a number of variables were added: of interest in this connexion is the date of stopping oral contraceptives or removal of an IUD. Information on maternal smoking habits in early pregnancy (0, <10 cigs/day, >10 cigs/day) and relative infertility (attempt at pregnancy >1 year) are also recorded. All this information is thus recorded prospectively for every pregnancy, at the time of the first visit to a maternity health centre (usually weeks 10–12).

Since 1965, there has been a detailed Registry of Congenital Malformations to which all infants with relatively severe malformations must be reported. The descriptive quality of that registry is much higher than that of the Medical Birth Registry and a detailed classification, based on X-ray reports, clinical descriptions and autopsy findings, can nearly always be made. The two registries can be linked using the personal identification number of the mother and the date of birth of the infant.

Two populations of infants were used. The larger population was based on all infants with an identified limb reduction defect (either in the Medical Birth Registry or in the Registry of Congenital Malformations) and born in 1983–1986. We identified 233 such infants, but 11 did not link with the Medical Birth Registry (reasonably, because of deficiencies in the identification numbers) and the study is thus restricted to 222 cases. These cases were compared with all births (n = 324 506) and the expected numbers of various exposures were calculated, stratifying for year of birth, maternal age (in 5 year bands), and parity (1, 2, 3, 4+). The observed numbers of exposures were compared with the expected numbers using a Poisson model.

The smaller infant population was restricted to severe limb reduction defects: amelia, phocomelia, femur-fibula-ulna reductions (FFU), and other combined long bone reductions. Such cases are relatively rare and all recorded cases in the Registry of Congenital Malformations for the period 1973–1981 which linked with the Medical Birth Registry were selected, a total of 57. For each case, two controls were selected from the Birth Registry with the following matching criteria: born at the same hospital and at the same time (± 2 months), and the same maternal age band and parity (1, 2, 3+). Among all eligible controls, two were selected randomly. During this time period, no information on oral contraceptives or smoking was computerised but the information was recorded in the maternity health record system. Copies of such maternity health records were requested from the delivery units for all cases and controls. Some hospitals did not submit copies, and in some cases, records for specific cases could not be traced. The final sample consisted of 36 complete triplets (case + two controls) and six pairs (case + control). In another three triplets, information was obtained only for one control but not for the case, in one triplet for both controls but no case. Thus information was available for a total of 42 cases (74%) and for 83 controls (73%).

The exposure frequency was determined for all available cases and controls. When statistical comparisons were made for the complete triplets and the pairs, relative risks and significance levels were determined by application of exact binomial distributions (p = 1/3 in complete triplets, 1/2 in pairs).

Results

ALL LIMB REDUCTION DEFECTS, 1983–1986

Table 1 specifies the types of limb reductions that were studied, whether they are restricted to one limb or not, and whether non-limb malformations were present in the infant or not. The table also specifies the 11 cases where no information was obtained because linkage failed.

Table 2 presents those cases where a date of removal of an IUD or cessation of oral contraceptives was known. Expected numbers from the total population are given within brackets. Each category of limb reduction defect and isolated *v* multiple forms are presented separately, but numbers in each group are low.

In only three cases was an IUD present or oral contraceptives continued into pregnancy—the expected number is 4·5. The risk ratio is thus 0·7 with a

Table 1 *Overview of infants with limb reduction defects, 1983–1986.*

Limb reduction type	*Isolated info*	*No info*	*Multiple info*	*No info*	*Total*
Transverse reductions					
Finger/toe reduction, one limb	59	3	8	1	71
> one limb	32	1	9		42
not specified	1				1
Other transverse reduction, one limb	39	2	3		44
> one limb	3				3
Other reductions					
Amelia or phocomelia, one limb	4		1	1	6
> one limb	2	1	1	1	5
Radial reduction, unilateral	1		2		3
bilateral	3		5		8
not specified			2		2
Ulnar reduction, unilateral			1		1
Tibial reduction, unilateral	1				1
bilateral			1		1
Fibular reduction, unilateral	5				5
bilateral	1				1
Femur reduction, unilateral	5	1			6
Femur-fibula-ulna syndrome	1				1
Patellar aplasia, unilateral	1		1		2
Combined reductions	1		1		2
Unspecified reduction					
Unspecified reductions, upper limb	15		2		17
lower limb	4				4
upper and lower limb	2		1		3
limb not stated	4				4
Total	184	8	38	3	233

Info: record linkage successful and data on various exposures available; Isolated: limb malformations only; Multiple: non-limb malformations as well.

Table 2 *Use of IUD or oral contraceptives in relation to LMP. The material is divided according to type of limb reduction defect and according to absence or presence of non-limb malformations. Observed numbers with expected numbers within parentheses calculated from the total population after stratification for year of birth, maternal age, and parity.*

Contraceptive practice	*Type of limb reduction*					
	Transverse	*Other*	*Unspecified*	*Isolated*	*Multiple*	*Total*
Intrauterine device						
After month of LMP	2 (1·3)	0 (0·3)	0 (0·2)	1 (1·6)	1 (0·3)	2 (1·9)
Month of LMP	0 (3·1)	0 (0·7)	0 (0·5)	0 (3·7)	0 (0·7)	0 (4·4)
1 month before LMP	4 (2·9)	0 (0·7)	0 (0·5)	3 (3·5)	1 (0·6)	4 (4·1)
2–3 months before LMP	6 (3·7)	0 (0·8)	1 (0·7)	6 (4·4)	1 (0·8)	7 (5·2)
4–6 months before LMP	3 (2·4)	0 (0·6)	0 (0·5)	2 (2·9)	1 (0·6)	3 (3·4)
> 6 months before LMP	3 (3·8)	1 (0·9)	0 (0·8)	3 (4·4)	1 (1·0)	4 (5·4)
Oral contraceptives						
After month of LMP	0 (1·7)	1 (0·5)	0 (0·3)	0 (2·2)	1 (0·4)	1 (2·6)
Month of LMP	6 (5·8)	3 (1·6)	0 (1·0)	8 (7·1)	1 (1·3)	9 (8·5)
1 month before LMP	6 (6·7)	3 (1·9)	1 (1·2)	9 (8·2)	1 (1·6)	10 (9·8)
2–3 months before LMP	12 (11·3)	4 (3·2)	2 (2·1)	15 (13·8)	3 (3·7)	18 (16·6)
4–6 months before LMP	5 (8·0)	4 (2·3)	0 (1·4)	7 (9·7)	2 (4·0)	9 (11·8)
> 6 months before LMP	7 (10·1)	3 (3·2)	6 (2·0)	13 (12·3)	3 (2·9)	16 (15·2)

95% CI of 0·1–1·9 (based on a Poisson distribution). Only one case had oral contraceptives in early pregnancy against 2·6 expected (risk ratio 0·4, 0·0–2·1). The number of cases with an IUD removed the month before LMP or later is 6 against 10·4 expected: risk ratio 0·6, 0·2–1·3. The number of cases stopping oral contraceptives the month before LMP or later is 20 against 20·9 expected, risk ratio 1·0, 0·6–1·5. As is seen from the table, no differences between observed and expected numbers are present, either for IUD, or for oral contraceptives, for the periods 2–3, 4–6, or > 6 months before LMP.

Among parents of infants with limb reduction defects, 14 couples had been involuntarily childless for at least one year. The expected number, estimated after stratification for year of birth, maternal age, and

parity, is 17·3. The relative risk is 0·8 with CI 0·4–1·6. At transverse reductions, the observed number is 11 and the expected number 11·8.

Table 3 presents data on smoking. There is no definite effect of smoking, either in the total set of data for all limb reduction defects, or in any of the subgroups. The relative risk for smoking *v* non-smoking is 1·1, its 95% CI is 0·8–1·4.

SEVERE LIMB REDUCTION DEFECTS, 1973–1981

Table 4 presents an overview of the material, divided according to limb reduction type.

Among the 42 cases, information on smoking in early pregnancy was present in 34, 15 of whom smoked (44%). Among the 83 controls, smoking information was available in 64, of whom 26 smoked (41%). The crude odds ratio is 1·2 ($\chi^2 = 0·3$, NS), and when calculated within triplets and pairs it is 1·0. Nine cases and 11 controls smoked more than 10 cigs/day: crude odds ratio 1·7 ($\chi^2 = 1·2$, NS), calculated within triplets/pairs, 1·4 ($p = 0·08$).

Seven women had stopped oral contraceptives within 6 months of LMP among the cases (17%); the corresponding figure for the controls is 16 (19%). This difference may be random. Only one woman had used oral contraceptives during pregnancy, a control. Three cases and four controls became pregnant within one month of stopping oral contraceptives, and two cases and nine controls within 2–3 months of stopping oral contraceptives.

Drugs in early pregnancy were reported by 21 of the 42 cases (25 drugs) and 21 of the 83 controls (24 drugs). The risk ratio (analysed within triplets and pairs) is 2·2 ($p = 0·002$). Four cases but no controls had used insulin. Six cases and only two controls had used analgesics (mainly salicylates), $p = 0·04$. If these two exposures are removed, no significant difference in drug use was seen between cases and controls (risk ratio 1·1, $p = 0·2$). None used a thyroid preparation. Two sex steroid exposures were recorded: one case (allyloestrenol) and one control (dydrogesterone). Anti-emetics were used by six case mothers (seven drugs) and nine control mothers (12 drugs). The diagnoses of the four infants born of diabetic women were:

1. Right sided femur and left sided fibula reduction, heart malformation.
2. Bilateral phocomelia of lower limbs.

Table 3 *Smoking habits in early pregnancy when known (93%). The material is divided according to type of limb reduction defect and according to absence or presence of non-limb malformations. Observed numbers with expected numbers within parentheses, calculated from the total population after stratification for year of birth, maternal age, and parity.*

	Type of limb reduction					
	Transverse	*Other*	*Unspecified*	*Isolated*	*Multiple*	*Total*
No smoking	100 (103·2)	26 (24·5)	15 (15·9)	115 (118·1)	26 (25·4)	141 (143·6)
< 10 cigs/day	26 (26·7)	7 (7·0)	6 (4·3)	33 (31·6)	6 (6·4)	39 (38·0)
> 10 cigs/day	21 (17·2)	3 (4·5)	2 (2·8)	22 (20·3)	4 (4·2)	26 (24·5)
Total	147	36	23	170	36	206

Table 4 *Overview of case-control material of severe limb reduction defects, born in 1973–1981.*

Diagnostic groups	*Total number*	*Affected limbs*		*With non-limb malformation*	*Complete triplets*	*Only case + control*	*Only control*	
		one	*> one*				*two*	*one*
a− or phocomelia	16	13	3	4	10	2		
FFU								
mainly femur	6	6			5			
mainly fibular	16	14	2	1	12	2		1
mainly ulnar	5	4	1	2	1	1		
femur + fibula	4	4		1	1	1	1	
ulna + fibula	1	1			1			
Other								
femur + tibia	4	4		1	3			1
fibula + tibia	3	3		1	1			1
transverse + phocomelia	1			1	1			
transverse + fibula	1		1		1			
Total	57	49	8	11	36	6	1	3

FFU = femur-fibular-ulna reductions

3. Right sided ulnar longitudinal reduction.
4. Right sided fibular reduction, syndactyly with digital reduction of foot, thoracic malformation.

Discussion

The most noteworthy finding in the present study is the absence of an association between oral contraceptive use in or just before pregnancy and limb reduction defects. This association has been described in at least three separate studies although the findings show some variation.[2 5 9] Various explanations for this discrepancy can be proposed.

Our negative finding may be random. It may hide a true risk but the upper 95% confidence limit indicates that it is probably no larger than 2·1 times (the 95% confidence interval of the Poisson distribution based on this observation is 0·02 to 5·57 and the expected number, calculated from a very large number of pregnancies, is 2·6). In the second sample of severe limb reduction defects, no instance of oral contraceptive use in early pregnancy was seen. The risks described from the USA[2] and Australia[9] should probably have been identified in our sample, if they existed. The moderate risk increase described from Hungary,[5] however, could have been missed.

Exposure information may be incomplete as it is based on medical chart information. The medical record form used specifically asks for the date of stopping oral contraceptives but this question may not be answered. Since information is collected prospectively (in early pregnancy), the existence of a limb reduction defect cannot influence the recording, but theoretically limb reduction defects may be associated with some factor which affects the completeness with which the recording is made. We can see no reasonable candidate for such a factor, since the recording of these dates probably largely depends on the midwife who performs the interview at the maternity health centre. We checked the information recorded in the register against the original records in a sample of 500 cases, and found that the information in the records of 157 women with dates of stopping oral contraceptives was correct in the registry in 97%.

All studies demonstrating significant associations between limb reduction defects and oral contraceptives are based on retrospective interviews, in some cases performed many years after the birth of the child. The possibility of a recall bias[9] cannot be disregarded.

The composition of the oral contraceptives used may differ in the different populations.

There are further possibilities. Use of oral contraceptives in early pregnancy reasonably means an unplanned pregnancy, perhaps unwanted. In Sweden, induced abortions are free and easily available and practically all strongly unwanted pregnancies are terminated. It is therefore likely that women who used oral contraceptives in early pregnancy but did not have an induced abortion had not planned a pregnancy but could accept it. Conditions were probably different in the other three populations studied. A new and strict abortion law was introduced in Hungary in 1974 and the cases analysed were collected from the period 1975–1977.[5] Also the American and Australian data were collected at a time when legally induced abortions were probably not as easily available as in Sweden. This could give a selection bias, if the increased risk for limb reduction defects is basically related to strongly unwanted pregnancies. A 2·1 times increased risk for limb reduction defects was found in extramarital births and an 1·5 times increased risk in unwanted pregnancies.[5] If such pregnancies to a large extent are terminated in Sweden, the association with oral contraceptives will not be demonstrable.

Janerich *et al*[2 13] stressed that the association found between limb reduction defects and oral contraceptive use could indicate a basic endocrine abnormality in the women which favoured conception soon after cessation of oral contraceptives as well as the occurrence of limb reduction defects. They pointed out the association between twinning and limb reduction defects and the increased rate of twinning described in pregnancies which started soon after cessation of oral contraceptives,[14] which was not found in another study.[15] An increased rate of twinning is known to exist in extramarital pregnancies, and it has been suggested that this is due to biological factors which increase the risk for an unwanted conception.[16]

In the present study, only a weak and non-significant association between smoking and limb reduction defects was found, and only for severe limb reductions. The only similar indication in the previous literature is the study of Aro[7] who also found a non-significantly increased risk for limb reduction defects in smoking women. In the few instances when maternal smoking has been shown to increase the risk for a malformation (cleft lip/palate[17 18]) the risk has been low and of the same magnitude as that registered in the present study. A larger sample population would be needed to prove such a weak effect.

Drugs were used significantly more often by women who had infants with severe limb reduction defects than by other women. The difference is due to two categories: insulin and analgesics. We found four women with insulin dependent diabetes among 42 women who had infants with severe limb reduction defects—this disease occurs at a rate of about 1/300 of delivered women in Sweden. In a cohort study of 1521

diabetic women who were delivered 1978–1981, seven infants with limb reduction defects were identified (expected number, one).[19] A suggested relationship was reported in one study[3] but was not found in another.[5]

The finding of an excess of analgesic use in early pregnancy among cases is astonishing. It was also found in another study[5] but the drugs were then mainly used after the first trimester. It seems rather unlikely that single aspirin tablets can cause limb reduction defects—the association (if not random) may be due to some unidentified confounder, eg, viral infections. An increased risk ratio for upper respiratory tract infections during the first trimester has been described.[7] We found no effects of any other drug, and specifically no indications of a role for thyroid drugs as previously described.[12] That finding, however, referred to any thyroid medication before pregnancy; we report only on thyroid drugs used in early pregnancy.

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