Acta Genet Med Gemellol 40: 325-335 (1991)

Received 5 June 1991
Final 21 October 1991

Conjoined Twins - An Epidemiological Study Based on 312 Cases

The International Clearinghouse for Birth Defects Monitoring Systems[1]

Abstract. Data on conjoined twins have been collected from 14 different malformation monitoring programs around the world. Among over 28 million births, 312 cases were identified. After considering underascertainment in one large program, the best estimate of the incidence based on the sum of induced abortions and births is 1.3 per 100,000 births. The distribution according to type of twinning, the sex distribution (39% males) and the stillbirth rate (47%) are presented. The presence of malformations not directly related to the area of fusion is discussed. In three women, thyroid disease was present and five women had been treated for infertility before conception.

Key words: Conjoined twins, Prevalence, Sex distribution, Drugs, Malformations

INTRODUCTION

Conjoined twins are extremely rare, with estimates of their prevalence at birth about 1:50,000. Some authors have reported a tendency for these events to cluster in time

[1]The following programs (program directors in parentheses) participated in the study: Australian Congenital Malformation Monitoring System (Paul A.L. Lancaster),Czechoslovakian Registry and Monitor of Congenital Malformations (Jirí Kučera), The Danish Registry of Congenital Malformations (Lisbeth B. Knudsen), Congenital Malformations Monitoring Program of England and Wales (Beverley J. Botting), Central-East France Register of Congenital Malformations (Elisabeth Robert), Paris Register of Congenital Malformations (Janine Goujard), Hungarian Congenital Malformation Registry (Csaba Elek), Italian Multicentric Register on Congenital Malformations, IPIMC (Pierpaolo Mastroiacovo), Emilia-Romagna Registry of Congenital Malformations, IMER (Guido Cocchi), New Zealand Congenital Anomalies Monitoring Program (Barry Borman), Medical Birth Registry of Norway (Lorentz Irgens), Latin American Collaborative Study of Congenital Malformations, ECLAMC (Eduardo Castilla), Spanish Collaborative Study of Congenital Malformations, ECEMC (María Luisa Martínez-Frías), The Swedish Registry of Congenital Malformations (Anders Ericson).

and/or space [eg, 1,9,14]. A recent analysis of data from South America [4] found two small clusters which, however, could be explained by statistical variation.

It is not known why, at the formation of monozygotic twins, there is an incomplete separation of the two body rudiments. Recently, it was suggested [17] that griseofulvin could be associated with the induction of conjoined twins. To test this hypothesis, data on conjoined twins were collected from 14 out of 25 members of the International Clearinghouse for Birth Defects Monitoring Systems. No cases exposed to griseofulvin were identified [10]. These data, the largest data set ever collected on conjoined twins, were updated and further analysed and reported in this paper. Part of the material has been published previously [4,13].

A similar association between conjoined twinning and maternal use of prochlorperazine has been published recently [2].

MATERIAL AND METHODS

The International Clearinghouse for Birth Defects Monitoring Systems was founded in 1974 and collects quarterly and annual data from members on the occurrence of malformations [cf 7]. At the present time, 25 different programs participate and they monitor some 3 million births annually. Although data on conjoined twins are not routinely reported to the Clearinghouse, each program records all types of malformations and it is therefore possible to collect information also on such a rare type as a conjoined twinning. However, only 14 programs participated in data collection and the total number of cases received was 312. For each case, information was requested on the year of birth, type of conjoined twinning, outcome of pregnancy (some programs included spontaneous or induced abortions), sex, detailed description of all recorded malformations, maternal age, previous deliveries. Some programs also submitted information on maternal drug usage in early pregnancy.

Terminology for conjoined twinning varies considerably. A common terminology was adopted from Broman [3] rather similar to that presented by Selby et al [19]. This simple terminology was selected in order to make it possible to classify at least the majority of the cases into some broad groups and analyse them jointly.

RESULTS

1. Prevalence at Birth

Table 1 shows the registered number of cases from each program and the rates per 100,000 births. The registered rates vary, partly due to small numbers. In some programs, induced abortions make up a considerable proportion of the cases. In one program (England-Wales), the rate is markedly lower than in the other large programs. The Figure shows the number of cases (including induced abortions) for each program plotted against the number of births. The unbroken line represents the mean rate after exclusion of the data from England-Wales (because of its obvious difference from the other materials, most probably due to larger underascertainment): 1.3 per 100,000 births

Table 1 - Number of conjoined twins and number of births according to monitoring program. Years of data collection are also given. Spontaneous and induced abortions are tabulated, but rates are based on births only

Program	Years	Number of conjoined twins			Number of births	Rate per 100,000 births[a]
		Spontaneous abortion	Induced abortion	Births		
Australia	82-88		1	21	1,684,768	1.25
Czechoslovakia	61-89			60	4,429,219	1.35
Denmark	83-88		1	4	328,305	1.22
England-Wales	74-88			62	9,565,241	0.65
Central-East France[b]	76-89		5	7	1,054,713	0.66
France: Paris	83-89		9	4	284,235	1.41
Hungary	70-90		6	38	3,213,480	1.18
Italy: IPIMC[c]	78-89			18	1,366,644	1.32
Italy: IMER[d]	78-88			4	195,703	2.04
New Zealand	82-88			4	362,055	1.10
Norway	67-89			11	1,322,291	0.83
South America[e]	67-89			27	2,283,999	1.18
Spain	76-89			12	747,400	1.60
Sweden	73-88	2	7	9	1,594,912	0.56
Total		2	29	281	28,432,965	0.99

[a] Refers only to conjoined twins born.
[b] Rhone-Alps-Auvergne-Jura region of France.
[c] IPIMC = Italian multicenter monitoring program, based on reports from 147 hospitals.
[d] IMER = Emilia Romagna region of Italy.
[e] Data from approximately 70 hospitals in Argentina, Bolivia, Brazil, Chile, Columbia, Ecuador, Paraguay, Peru, Uruguay, and Venezuela.

(1:78,000). The dotted lines give the approximate 95% confidence interval. It can be seen that all programs but England-Wales may estimate that common rate. If only births of conjoined twins are counted, the rate is 1.2 per 100,000 (1:86,000).

2. Type of Conjoined Twinning

Table 2 presents the distribution of types, divided into four main categories and a fifth one, unspecified, which makes up 21% of all.

The first main group is made up of parasitic twins, that is, when one of the twins is rudimentary. Only 6% of twins of known type are parasitic, but it should be stressed that such cases were only reported from five programs (Table 3) and may not have been registered as conjoined twins in other programs. They represent 16% of the cases reported from the five programs.

https://doi.org/10.1017/S0001566000003512 Published online by Cambridge University Press

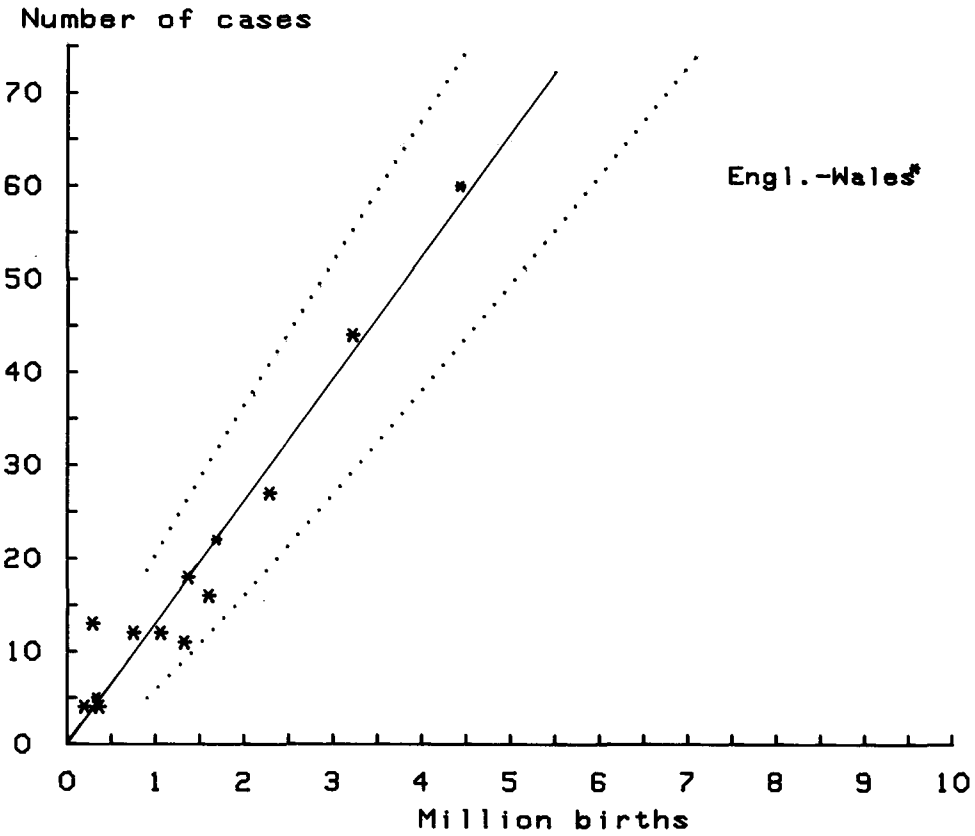

Figure. Diagram showing number of conjoined twins registered in each program plotted against the total number of births in that program and marked with *. The average rate of all programs, except for England-Wales, is shown as an unbroken line and its 95% confidence interval is marked with dotted lines.

The second main group is called conjunctio inferior, that is, the two bodies are fused from the caudal end. The 78 cases represent one third of those which are specified with respect to type and the majority (56) are variants of dicephalus, that is, two heads on a more or less single trunk. The remaining cases have also part of the trunk duplicated.

The third group is made up of twins conjoined in the middle part of the body with duplicated upper and lower parts: conjunctio media. They represent half of alla specified cases and the vast majority are thoracopagus twins, this being the most common of all specified types.

The fourth group consists of twins joined in the upper parts of the body but duplicated caudally: conjunctio superior. Only 12% of all specified types belong to this category, most of them are cephalothoracopagus.

The distribution of the main groups according to program is seen in Table 3 and according to pregnancy outcome in Table 4. It can be seen that the unspecified types make

Table 2 - Type of twinning (divided into main groups) and pregnancy outcome

Type of conjoined twinning		Spontaneous abortion	Induced abortion	Births	Total
Main group	Detailed type				
Parasitic	Epignatus	0	0	3	3
	Craniopagus parasiticus	0	0	2	2
	Thoracopagus parasiticus	0	0	4	4
	Dipygus parasiticus	0	0	3	3
	Unspecified	0	1	1	2
Conjunctio inferior	Pygopagus	0	0	9	9
	Ischiopagus	0	0	6	6
	Ileothoracopagus	0	0	7	7
	Dicephalus	0	6	38	44
	Dicephalus, tri/tetrabrachius	0	1	3	4
	Diprosopus	0	0	8	8
Conjunctio media	Xiphopagus	0	0	3	3
	Thoracopagus	0	12	79	91
	Prosopothoracopagus	0	0	2	2
	(Thoraco) Omphalopagus	1	3	25	29
Conjunctio superior	Craniopagus	0	2	9	11
	Cephalothoracopagus	1	1	11	13
	Dipygus	0	1	4	5
Unspecified type		0	2	64	66

Table 3 - Type of conjoined twinning according to program. Types divided into main groups (see Table 2)

Program	Parasitic	Conjunctio inferior	Conjunctio media	Conjunctio superior	Unspecified type
Australia	0	7	6	1	8
Czechoslovakia	7	17	24	6	6
Denmark	0	2	0	2	1
England-Wales	0	8	7	3	44
Central-East France[a]		2	8	2	0
France: Paris	1	3	6	2	1
Hungary	3	12	25	4	0
Italy: IPIMC[a]	0	3	13	2	0
Italy: IMER[a]	1	0	2	1	0
New Zealand	0	0	2	1	1
Norway	0	4	3	0	4
South America[a]	2	12	10	3	0
Spain	0	3	9	0	0
Sweden	0	5	10	2	1
Total	14	78	125	29	66

[a] See explanatory foot-notes of Table 1.

https://doi.org/10.1017/S0001566000003512 Published online by Cambridge University Press

up a high proportion of the cases reported from England-Wales (71%), Norway (4 out of 11), Australia (36%), and about 10% of the cases reported from Czechoslovakia. Table 4 shows that a very high percentage of the conjoined twins are stillbirths: among 254 infants where the status (stillbirth of livebirth) was known, 120 were stillborn (47%).

Table 4 - Type of conjoined twinning according to pregnancy outcome. Types divided into main groups (see Table 2)

Pregnancy outcome	Parasitic	Conjunctio inferior	Conjunctio media	Conjunctio superior	Unspecified type
Spontaneous abortion	0	0	1	1	0
Induced abortion	1	7	15	4	2
All births	13	71	109	24	64
Stillbirth	9	31	46	12	22
Livebirth, dead	3	13	32	6	6
alive	0	1	2	0	0
not specified	1	16	21	5	28
Birth not specified	0	10	8	1	8

3. Sex Distribution

Table 5 summarizes infant sex, when known. For the total material, there is a lowered sex ratio: only 39% of the cases were males against the expected 51%, and the 95% confidence interval indicates that this is probably not a random finding. There is an increased sex ratio in two groups: parasitic twins and conjunctio superior, but as can be seen from the tabulated confidence intervals, all groups may have the average sex ratio.

Table 5 - Sex distribution according to type of twinning (main groups according to Table 2). Only cases with known sex

Type of twinning	Males	Females	Proportion of males	
			%	95% CI
Parasitic	9	5	64.3	35.1-87.2
Conjunctio inferior	27	37	42.2	29.9-55.2
Conjunctio media	30	74	28.8	20.1-37.6[a]
Conjunctio superior	13	12	52.0	31.3-72.2
All types	93	146	38.9	32.7-45.1

[a] Calculated after normal approximation.

https://doi.org/10.1017/S0001566000003512 Published online by Cambridge University Press

4. Triplets

In at least 9 cases, the conjoined twins had a normal "triplet": 3 were reported from England-Wales, 2 from Hungary, and 1 case each from France (Paris), Italy (IPIMC), Norway, and South America. As maternal age distribution and the age-specific twinning rates for each program is not known, the expected number is difficult to calculate, but generally speaking twinning occurs at a rate of about 1:120 pregnancies and one would only expect 3 pregnancies with a free "triplet" in the present material. The observed number of 9 may also be underestimated, as the presence of a free "triplet" may not have been recorded in all instances.

5. Drugs Used

Information on drug usage during pregnancy was collected from most programs but was not available for all cases: no such information was available from Australia, England-Wales, or New Zealand.

In many instances, information existed on drug usage, but without specification of when the drug was used. The formation of conjoined twinning is a very early embryonic event and drugs taken later than the 5th week after the last menstrual period can have no causal significance. It can be noted, however, that many women had been treated with sex steroids later during pregnancy. They were identified in those programs where still sex steroid treatment is used, usually as support at the occurrence of bleedings in early pregnancy. This is very well demonstrated in the Hungarian material, where sex steroids had been used by 10 women (26%) – only one woman had started with the drug as early as week 5. This high rate may mirror a high usage of sex steroids during pregnancy in Hungary, but perhaps also an increased rate of early bleedings at conjoined twinning which would be a reason for the hormone treatment.

The following comments can be made on drugs used very early in pregnancy or preconceptionally.

Three women were under treatment with thyroid drugs (one from Czechoslovakia, two from Sweden) and a fourth woman had a goiter, but was not treated with thyroid drugs during pregnancy (Italy: IPIMC). Four women were treated with fertility drugs (one Czechoslovakia, three Central-East France) and one further case had been operated because of a Stein-Löwenthal condition in order to become fertile (Czechoslovakia).

Other early drug treatments are represented by only single instances for each drug. No exposure for prochlorperazine was noted.

6. Concomitant Malformations

The concept of concomitant malformations is a difficult one: what is a direct consequence of the conjoining process and what is actually a concomitant malformation? We have tried to remove all malformations that are directly related to the twinning process, but also this is difficult. Table 6 summarizes the main findings.

Fourteen of the cases showed anencephaly. In 3 of them, the type of twinning was not specified, among the other case 9 were dicephalics and 2 thoracopagus. Spina bifida or encephalocele occurred in 13 cases.

Table 6 - Concomitant malformations according to main type of twinning (see Table 2).

Concomitant malformation	Parasitic	Conjunctio inferior	Conjunctio media	Conjunctio superior	Unspecified
Anencephaly		9	2		3
Encephalocele or spina bifida	1	4	4	2	2
Facial cleft	1	5	13		
Esophageal or gut atresia		3	6	1	
Transposition of great vessels		3			
Diaphragmatic hernia		3	1		
Gastroschisis	1	3		1	2
Omphalocele	1	3		1	1
Severe kidney malformation		3	3	1	
Limb reduction		2	2	1	1
Total number with malformation descriptions	8	35	51	14	43

Other malformations that occurred in many cases were facial clefts, esophageal, anal or intestinal atresia, diaphragmatic hernia, gastroschisis, and omphalocele. Severe kidney malformations were seen in 7 cases. Finally, limb reductions were found in 6 cases.

DISCUSSION

Conjoined twinning is very rare and is the result of a monozygotic twinning where the two primitive embryonic rudiments (either inner cell masses or primitive streak structures) do not separate completely with a fusion of body parts as a result. A cranial duplication (dicephaly) may be caused by a splitting of the head process with two cranial body parts developing. From these international data we estimate the prevalence at birth to be around 1.3 per 100,000 births, but a marked variation was seen in different monitoring registries, from 0.6 to 2.0 per 100,000 births. This may to a large extent be due to small numbers.

There may be varying levels of ascertainment across the programs. Data indicate that this is most probably true for England-Wales but that all other programs may estimate the same average rate. Definitions may vary: it can be noted (Table 2) that parasitic twins were registered in only five programs and it is likely that an epignathus, for instance, has not been coded as a case of conjoined twinning in some other programs (which it undoubtedly is).

The definition of a stillbirth varies from 16 weeks (Norway) to 20 weeks (Australia), 500 g (Spain, South America), 180 days (Italy, France: Paris), 28 weeks (other programs). Two cases of late spontaneous abortions were described in the Swedish material but not included in the rate calculations – they may well have been recorded as stillbirths in some other programs. When intense prenatal screening is undertaken (as in Denmark, France and Sweden), some instances of conjoined twinning will be detected and aborted. In the two French programs, for instance, of the 25 identified cases, 14 were selectively aborted; among 16 Swedish cases, 7 were identified prenatally and aborted – and all selective abortions are not known in this population. It can be noted that the rate in Sweden for the period 1965-1974, and based on similar sources, was stated as 1.14 per 100,000 births [8], which is higher than that found in the period presented here (1973-1988, 0.56 per 100,000). This may be an effect of prenatal diagnosis followed by selective abortion. In the present analysis, the cases identified prenatally and aborted were included at the rate circulations – this may give an overestimate as some of these cases would probably have aborted spontaneously if no selective abortion had been performed.

The estimated prevalence at birth is lower than that often stated in the literature. Such estimates were, however, usually obtained from hospital series, often selected because of the occurrence of a couple of cases, and may overestimate the true prevalence. Our estimate is somewhat higher than that recorded (1:100,000) from the Birth Defect Monitoring Program in the USA [6].

A considerable proportion of the cases were not specified to type. This is especially true for some programs (eg, England-Wales). It should be remembered that the programs involved in the study are primarily monitoring programs, and for that purpose the type of twinning is of less importance.

The present material supports the general opinion that the most common type of conjoined twinning is made up of twins joined in the middle part of the body, notably thoracopagus and (thoraco-)omphalopagus. A large proportion is represented by upper duplications, notably dicephalus. There seems to be no significant variation in the main grouping of cases between programs, with the exception, already commented upon, that parasitic twins have been included only by some programs.

The stillbirth rate is very high and seems not to vary significantly with type. Our rate of 47% is higher than that recorded by Edmonds and Layde [6], 39%, but the difference may be random and the rate is also affected by stillbirth definitions used. The low sex ratio described in the literature for conjoined twins is verified in the study – there are differences in sex ratio according to main type but these may be random. A low sex ratio in all monozygotic twins (and notably in monoamniotic ones) has been described [5].

A recent paper discussed from developmental field aspects the origin of malformations directly associated with the area of fusion [12]. Also outside the area of fusion, an increased rate of malformations are seen. Edmonds and Layde [6] described such malformations in half of the 81 conjoined twins presented. The exact percentage depends to a large extent on inclusion criteria.

The present material describes the presence of malformations, not thought to be directly associated with the fusion of the two bodies. The selection of malformations not related to the fusion process is, however, arbitrary. For example, 14 cases of anencephaly were observed, 9 in dicephalic twins. It can be argued, that the two bodies of dicephal-

ic twins are fused completely, except for the heads (and then anencephaly lies outside the area of conjoined twinning), but it is more reasonable to argue that the two heads are caused by a splitting of the head process with one relatively normal body, and that the anencephaly is located to the malformed part of the body. This is obviously so at diprosopus – two of the anencephaly cases occurred in diprosopus twins.

Thirteen sets of conjoined twins had other neural tube defects, not directly related to the fusion area of the bodies. As neural tube development is directly regulated by the head process, it seems understandable that a disturbance of this process can cause a neural tube defect.

Facial clefts occur in 19 cases, 13 of them at conjunctio media, that is, when the heads are not involved in the fusion. It can also be noted that facial clefts are generally not increased in rate in free monozygotic twins [8,11], but an increased rate of facial clefts in twins has been described [15]. We found diaphragmatic hernia and abdominal wall defects in many cases also when the area of fusion was not in the thoracoabdominal region – notably, gastroschisis, which is usually an isolated malformation, was found in 4 cases. An increased rate of multiple births has been described at gastroschisis from Australia [16].

Esophageal, anal or gut atresia, and severe kidney malformations were seen in many conjoined twins. Also limb reductions of various types were common. Together, these malformations enter the concept of the VATER association. An increased rate of these malformations has been described in twins [8] and it was then speculated that this could be an effect of the central primary mesoderm disturbance thought to cause monozygotic twinning and notably conjoined twinning.

A seemingly high number of triplet pregnancies, two of the triplets forming the case of conjoined twins, was found. This has been described previously in the literature [18].

Data on exposures which could be related to conjoined twinning are sparse, but at least two phenomena can be noted which may be important. One is the presence of thyroid disease in some of the women, the other is the treatment for infertility which had been made in some cases. It is difficult to say whether the underlying endocrinological or other problems can somehow increase the risk for a maldevelopment of monozygotic twins. A reference can be made to the hypothesis [20] that the cause of the maldevelopment can be sought in an overripeness of the egg due to delayed ovulation.

This study exemplifies the utilization of a large data base for the study of a rare malformation like conjoined twinning. The material was originally collected in order to test a hypothesis, an association between the use of a specific drug (griseofulvin) and conjoined twinning. The prerequisite for such a study is the existence of ongoing registration of congenital malformations and an organization such as the International Clearinghouse for Birth Defects Monitoring Systems which makes a collaboration between various programs practically possible.

REFERENCES

1. Bheattay E, Nelson MM, Beighton P (1975): Epidemic of conjoined twins in southern Africa? Lancet ii:741.
2. Brambali B, Lanzani A, Sanchiani L, Tulin L (1990): Conjoined twins and inutero early exposure to prochlorperazine. Reprod Toxicol 4:331-332.
3. Broman I (1911): Normale and Abnorme Entwicklung des Menschen. Wiesbaden: J.F. Bergman Verlag.
4. Castilla EE, Lopez-Carmelo JS, Orioli IM, Sánchez O, Paz JE (1988): The epidemiology of conjoined twins in Latin America. Acta Genet Med Gemellol 37:111-118.
5. Derom C, Vlietnick R, Derom R, van den Berghe H, Thiery M (1988): Population-based study of sex proportion in monoamniotic twins. New Engl J Med 319:119.
6. Edmonds LD, Layde PM (1982): Conjoined twins in the United States, 1970-1977. Teratology 25:301-308.
7. International Clearinghouse for Birth Defects Monitoring Systems (1991): Congenital Malformations Worldwide. Amsterdam, New York, Oxford: Elsevier, ISBN 0444 89137 Y.
8. Källén B (1986): Congenital malformations in twins: A population study. Acta Genet Med Gemellol 35:167-178.
9. Källén B, Rybo G (1978): Conjoined twinning in Sweden. Acta Obstet Gynecol Scand 57:257-259.
10. Knudsen LB (1987): No association between griseofulvin and conjoined twinning. Lancet ii:1097.
11. Little J, Bryan E (1986): Congenital anomalies in twins. Seminars in Perinatology 10:50-64.
12. Machin GA, Sperber GH (1987): Invited editorial comment: Lessons from conjoined twins. Amer J Med Genet 28:89-97.
13. Metneki J, Czeizel A (1989): Conjoined twins in Hungary, 1970-1986. Acta Genet Med Gemellol 38:285-299.
14. Milham S Jr (1966): Symmetrical conjoined twins: An analysis of the birth records of twenty-two sets. J Pediatr 69:643-652.
15. Myrianthopoulos NC (1976): Congenital malformations in twins. Acta Genet Med Gemellol 25:331-335.
16. National Perinatal Statistics Unit, University of Sidney (1988): Congenital Malformations Monitoring Report. March 1988. ISSN 0726-4046.
17. Rosa FW, Hernandez C, Carlo WA (1986): Griseofulvin teratology, including two thoracopagus conjoined twins. Lancet i:171.
18. Schinzel AAGL, Smith DW, Miller JR (1979): Monozygotic twinning and structural defects. J Pediatr 95:921-930.
19. Selby LA, Khaalili A, Stewart RW, Edmonds LD, Marienfield CJ (1973): Pathology and epidemiology of conjoined twinning in swine. Teratology 8:1-10.
20. Witchi E (1934): Appearance of accessory "organizers" in overripe eggs of the frog. Proc Soc Exp Biol Med 31:419.

Correspondence: Professor Bengt Källén, Department of Embryology, Biskopsgatan 7, S-223 62 Lund, Sweden.