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## Lethal malformations and perinatal mortality: a 10 year review with comparison of ethnic differences

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### Abstract

During 1976 to 1985 perinatal mortality in Leicestershire decreased from 21 to 9.5 per 1000 births. Throughout this period the incidence of lethal malformations, excluding neural tube defects, remained relatively constant at around 1.8 per 1000 births. Analysis of the malformations present in 201 lethally malformed babies showed that 147 (73%) had a disorder carrying a recurrence risk of 1% or greater. Only 7% of these malformations might have been predicted from the family history or advanced maternal age. The incidence of lethal malformations was significantly increased in the Asian population, largely because of an excess of autosomal recessive disorders.

The contribution of lethal malformations to perinatal mortality has almost doubled over the past 10 years and is likely to increase despite prenatal diagnosis and improvements in obstetric and paediatric services.

### Introduction

Malformations account for a substantial proportion of perinatal mortality in the United Kingdom, with figures of 26% and 34% having been observed in recent studies.<sup>1,2</sup> Given the decline in other causes of perinatal death and the recent unexplained reduction in the incidence of neural tube defects,<sup>3</sup> attention will probably focus increasingly on babies with malformations other than neural tube defects, whose relative contribution to perinatal mortality is likely to increase despite existing or planned improvements in obstetric and paediatric services.

In 1976 a comprehensive survey of perinatal mortality was launched in Leicestershire (population 833 000), a county which readily lends itself to epidemiological study as obstetric and paediatric services are based in two centrally located teaching hospitals, thus facilitating the collection of relevant information. Using data from the first 10 years of this survey we reviewed the

records of babies dying as a result of malformations, excluding neural tube defects. The objectives of this study were (a) to ascertain whether there had been any change in the overall incidence of lethal malformations over 10 years; (b) to establish the aetiological range and its genetic component; (c) to estimate the possible impact of genetic counselling and prenatal diagnostic surveillance; and (d) to identify possible ethnic differences.

### Methods

Babies were ascertained through the records of the Leicestershire perinatal mortality survey, full details of which have been recorded elsewhere.<sup>4,5</sup> Strenuous efforts were made to review the records of all babies along with necropsy reports, radiographs, and clinical photographs. Babies were included in the study only if death was due primarily to a malformation, so that babies who had a relatively minor abnormality, which was coincidental rather than causally related to their death, were not included. When appropriate recourse was made to expert opinion and the London dysmorphology database to help establish the diagnosis.<sup>6</sup>

The results presented below refer to lethal malformations other than isolated non-syndromic neural tube defects.

### Results

#### INCIDENCE OF LETHAL MALFORMATIONS

Table I gives the birth statistics for Leicestershire for 1976-85. During this period 208 babies died in the perinatal period primarily as the direct result of a malformation or malformations: an overall incidence of 1.80 per

TABLE I—Birth statistics for Leicestershire 1976-85

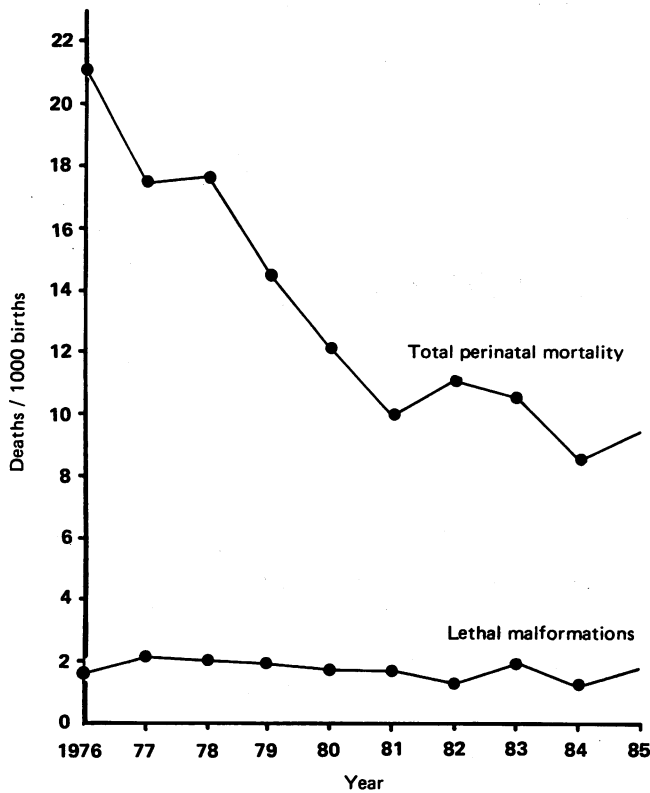
	Deaths due to malformations			Total perinatal deaths	Total births		
	White	Asian	Total		White	Asian	Total
1976	15	3	18	230	9 752	1 123	10 875
1977	20	4	24	190	9 549	1 286	10 835
1978	19	4	23	196	9 784	1 276	11 060
1979	19	4	23	172	10 388	1 366	11 754
1980	18	4	22	151	10 822	1 524	12 346
1981	16	5	21	118	10 273	1 518	11 791
1982	12	4	16	130	10 061	1 496	11 557
1983	16	7	23	122	9 979	1 565	11 544
1984	11	4	15	101	10 161	1 625	11 786
1985	18	5	23	114	10 375	1 582	11 957
Total	164	44	208	1524	101 144	14 361	115 505

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1000. Although the number of babies dying as a result of malformations remained relatively constant throughout the study period, the overall perinatal mortality rate fell from 21 per 1000 in 1976 to 9.5 per 1000 in 1985. These trends are shown in the figure.



Overall perinatal mortality and contributing lethal malformations, excluding neural tube defects, in Leicestershire 1976-85.

#### CAUSES AND GENETIC CONTRIBUTION

The hospital records of 201 of these babies were reviewed. For 21 babies no clear diagnosis could be established, either because investigation or documentation, or both, were incomplete or because the pattern of abnormalities did not match any known disorder or syndrome.

Table II shows that most of the remaining 180 babies had a disorder that was at least partly genetic in origin—that is, chromosomal, single gene, or multifactorial. Thirty eight (21%) babies had a chromosomal abnormality, and 24 (13%) had a known autosomal recessive disorder (table III). In addition 12 (7%) babies had disorders showing aetiological heterogeneity; this may include recessive inheritance—that is, renal dysplasia, diaphragmatic agenesis, lissencephaly, and ill defined short limbed dwarfism. Disorders showing multifactorial inheritance or known to convey a recurrence risk of 1% or greater, accounted for 73 (41%) deaths. A non-genetic aetiology could be established with certainty in only 23 (13%) of the 180 study babies with a known diagnosis, although an additional 10, indicated in table II as having a recurrence risk of less than 1%, almost certainly had a non-genetic cause.

#### POTENTIAL FOR PREVENTION

The 180 study babies contained four sibling pairs, three with an autosomal recessive disorder (Meckel's syndrome, multiple pterygia and polycystic kidneys) and one with an inherited chromosome abnormality. There were also three babies with an affected sibling born before 1976 in whom the diagnoses were idiopathic hydrops, Robert's syndrome, and diaphragmatic agenesis. The father of one baby with trisomy 18 had a child with trisomy 21 in a previous marriage, and one baby with complex congenital heart disease had an older sibling with corrected transposition of the great vessels. Thus nine (5%) of the study babies had a family history of abnormality, so that it could be argued that these nine births were "preventable." In addition,

TABLE II—Cause of death of babies in the study (recurrence risks(%) in parentheses)

	White		Asian	
	No	Rate/10000	No	Rate/10000
<b>Chromosomal:</b>				
Trisomy 13 (1.3)	8	3.2	0	4.2
Trisomy 18 (1.3)	13		2	
Trisomy 21 (1.3)	5		1	
Other, inherited (5-10)	2		2	
Other, de novo (1.3)	4		1	
<b>Single system:</b>				
<b>Cardiac</b>				
Hypoplastic left heart (2)	11	3.5	3	4.9
Complex (1)	8		1	
Isomerism (4-5)	3		1	
Other (1-4)	13		2	
<b>Renal*</b>				
Bilateral agenesis (3-8)	8	1.7	4	4.9
Polycystic kidneys (25)	3		2	
Dysplastic kidneys (1-25)	3		0	
Urethral obstruction (<1)	3		1	
<b>Pulmonary</b>				
Diaphragmatic hernia (2)	9	1.3	1	0.7
Diaphragmatic agenesis (2-25)	3		0	
Pulmonary hypoplasia (<1)	1		0	
<b>Skeletal (2-25)</b>				
Gastrointestinal (<1)	8		2	
<b>Cerebral</b>				
Hydrocephalus (3)	4	1.0	0	0.7
Holoprosencephaly (6)	3		0	
Other (0-5)	3		1	
<b>Multisystem recessive syndromes† (25)</b>				
	3	0.3	11	7.7
<b>Miscellaneous non-genetic‡ (&lt;1):</b>				
Amniotic bands	3	1.6	2	4.9
Twin-twin disruption	2		2	
VATER association	7		2	
Cloacal abnormality	2		0	
Sirenomelia	1		1	
Hydrops (cytomegalovirus infection)	1		0	
Cause unknown (?)	20		1	
Notes unobtainable (?)	7		0	
<b>Total§</b>	<b>164</b>	<b>16.2</b>	<b>44</b>	<b>30.6</b>

\* $\chi^2=6.15$ ;  $0.01 < p < 0.02$ . † $\chi^2=56.27$ ;  $p < 0.001$ . ‡ $\chi^2=6.84$ ;  $p < 0.01$ . § $\chi^2=14.49$ ;  $p < 0.001$ . Comparisons are of white v Asian babies.

TABLE III—Babies in the study with a definite autosomal recessive disorder

	White	Asian
<b>Multisystem syndrome:</b>		
Meckel	1	6
Multiple pterygia		3
Pena Shokair		1
Robert's	1*	
Smith-Lemli-Opitz II	1	
Hydrops		1*
<b>Single system disorder:</b>		
Polycystic kidneys	3	2
Diaphragmatic agenesis	1*	
Campomelic dysplasia	3	
Saldino Noonan	1	
<b>Total</b>	<b>11</b>	<b>13</b>
<b>Rate/10000†</b>	<b>1.09</b>	<b>9.1</b>

\*Previously affected sibling. † $\chi^2=38.09$ ;  $p < 0.001$  (white v Asian babies).

three of the mothers of babies with non-disjunction were aged 38, 39, and 39 years, so these three births, each affected by trisomy 18, might also be deemed "preventable."

#### ETHNIC DIFFERENCES

From tables I and II it is clear that there was a highly significant difference in the death rates due to malformations between babies born to white mothers and those born to mothers of Asian (mainly Indian subcontinent) origin. This was most striking for autosomal recessive disorders (table III). Six of the 13 babies with a definite autosomal recessive disorder born to Asian parents were known to have consanguineous parents (four Moslem and two Hindu). Five had non-consanguineous Hindu parents, and the

remaining two were born to a Hindu couple and a Moslem couple for whom details of consanguinity were not available.

The other significant differences were for renal abnormalities and miscellaneous non-genetic conditions. When the two babies with polycystic kidney disease born to consanguineous Asian parents were excluded a comparison of the number of babies with renal disorders (17 white *v* five Asian) was no longer significantly different ( $\chi^2=2.10$ ;  $p=0.1$ ). Two of the seven Asian babies in the miscellaneous non-genetic group were born to Hindu parents (one with amniotic bands and one with the VATER association (vertebral defects, anal atresia, tracheo-oesophageal fistula, radial and renal dysplasia)) and two to Moslem parents (one with amniotic bands and one with the VATER association). The remaining three Asian babies were delivered to Sikh parents: one of these babies had sirenomyelia while the other two had gross structural disruptive defects resulting from artery-artery anastomoses in twins.

## Discussion

These results show that, although the incidence of lethal malformations has remained relatively constant over 10 years, their contribution to perinatal mortality has increased from 10% in 1976-7 to 18% in 1984-5. It is disappointing that the recent unexplained decline in the incidence of neural tube defects has not occurred with other lethal malformations. Presumably this is due, at least in part, to amelioration of the poorly understood environmental factors that contribute to neural tube defects, whereas the sizeable genetic component in other lethal malformations has remained unchanged.

Our results confirm previous studies in showing a major genetic contribution to lethal malformations.<sup>7,9</sup> Of the 201 babies in the study whose records were available for review 147 (73%) had a disorder with a recurrence risk of 1% or greater. When the 21 babies in whom no diagnosis could be established were excluded this proportion rose to 82%, a figure that corresponds closely to that of 79.5% obtained in an American study.<sup>9</sup> This shows the importance of full assessment and investigation of these infants.<sup>10</sup> Experience in Leicester suggests that this is a worthwhile exercise. Twenty of the 21 undiagnosed cases in this survey came from the first seven years of the study period, with only one from the last three years.

The existence of a lethal malformation might have been predicted on the basis of family history or advanced maternal age in only 12 (7%) of the babies, so that even the most enthusiastic prenatal diagnostic programme would have had little effect on overall perinatal mortality. The introduction of routine diagnostic ultrasonography during the second trimester, as advocated by Campbell and Smith,<sup>11</sup> would be expected to detect about half of these cases—that is, those with major structural abnormalities of the brain, heart, kidneys, or skeleton. This development, however, will not be easily achieved on a large scale in an atmosphere of economic stringency, nor will it necessarily be welcomed by all parents and doctors.

Increased perinatal mortality rates in Asian populations have been noted elsewhere in the United Kingdom and are likely to be due to a combination of social, environmental, and genetic factors.<sup>12</sup> The increased incidence of lethal malformations in babies of Asian origin noted in this study can be attributed largely to an excess of autosomal recessive disorders, chiefly Meckel's syndrome, which seems to be particularly common in Gujaratis,<sup>13</sup> plus other rare

recessive syndromes, which in many instances are the consequence of consanguineous relationships. Several groups in Britain are looking prospectively at the morbidity and mortality associated with consanguineous marriages in British ethnic minorities, although it may be that the social and family benefits of consanguinity outweigh its possible deleterious genetic effects.

Not all of the excess mortality in the Asian babies, however, can be attributed directly to genetic factors as there was also a significant excess of non-genetic lethal malformations in the Asian group. Most of these babies were born to Hindu and Sikh parents, who rarely practise consanguinity. Thus it is unlikely that rare recessive disorders have been misdiagnosed as non-genetic conditions. The Birmingham studies have also noted an excess of malformations in the non-consanguineous Indian population, so that social and environmental factors such as diet may be influential.<sup>12,14</sup>

This study confirms that the contribution of lethal malformations to perinatal mortality has almost doubled over the past 10 years, and presumably will continue to rise if further inroads are made into the prevention of other causes of death in the perinatal period. This, combined with the substantial genetic element in the aetiology of these malformations and its associated implications for future pregnancies, shows the importance of assessing these babies, both individually and on a larger scale, as an important component of perinatal mortality surveys.

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