

FETAL AND INFANT MORTALITY ASSOCIATED WITH CONGENITAL MALFORMATIONS

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With the decline in mortality from other causes, congenital malformations represent an increasingly important cause of stillbirth and infant death. Malformations are also an important cause of spontaneous abortion and this paper examines the high fetal and infant loss associated with these conditions, using data collected on all births in 1964-66 to women resident in South Wales. The birth population and the ascertainment methods used in the survey have been described elsewhere (Richards and Lowe, 1971). Information on maternal age, parity, previous abortions, and parental occupation

relating to all births in the survey years was abstracted from birth notification forms on to coding cards for punching and analysis. The Registrar General of England and Wales supplied photocopies of the registrations of all stillbirths and infant deaths occurring in South Wales among infants born in the three years of the survey; while it is possible that some deaths occurred outside the survey area, their number is likely to be so small as to have a negligible effect on the infant mortality rates reported here.

TABLE I
ABORTIONS AMONG PREVIOUS PREGNANCIES ACCORDING TO TYPE OF MALFORMATION

Type of Malformation	No. of Malformed Infants	No. of Previous Pregnancies	No. of Previous Abortions	Abortions as Percentage of All Previous Pregnancies	Significance
Central nervous system					
Anencephaly	281	408	65	15.9	*
Spina bifida and cranium bifidum	356	571	101	17.7	***
Hydrocephalus (alone)	82	137	13	9.5	
Total	719	1,116	179	16.0	***
Heart and great vessels					
Patent ductus (alone)	38	68	18	26.5	**
Septal defects (alone)	73	113	22	19.5	*
Other specified defects	170	315	50	15.9	
Unspecified defects	117	184	29	15.8	
Total	398	680	119	17.5	***
Alimentary system					
Cleft lip (alone)	53	81	16	19.8	
Cleft lip with cleft palate	59	70	6	8.6	
Cleft palate (alone)	75	121	14	11.6	
Total	187	272	36	13.2	
Pyloric stenosis	196	227	12	5.3	**
Atresias	93	167	27	16.2	
Limb and skeletal system†					
Dislocation of hip	77	100	23	23.0	**
Talipes equinovarus	112	149	21	14.1	
Talipes, all cases	311	332	58	17.5	**
Polydactyly	93	167	26	15.6	
Urogenital system					
Hypospadias	113	143	24	16.8	
Other defects	129	170	29	17.1	
Total	242	313	53	16.9	*
Skin defects					
Vascular	193	268	38	14.2	
Others	175	277	27	9.7	
Total	368	545	65	11.9	
Other malformations					
Down's syndrome	90	243	38	15.6	

† Excluding cases of spina bifida

Significance levels: P < 0.05 *
P < 0.01 **
P < 0.001 ***

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TABLE II
MALFORMATION RATES RELATED TO PARITY AND PREVIOUS ABORTIONS

	No. of Previous Abortions	Maternal Parity			Total
		0	1	2 and over	
No. of births	0	29,774	23,685	24,714	78,173
	1	1,879	2,605	4,778	9,262
	2	295	553	1,076	1,924
	3	102	202	539	843
	Total	32,050	27,045	31,107	90,202
All malformations*	0	3.9 (1,161)	3.1 (734)	3.2 (791)	3.4 (2,686)
	1	4.8 (90)	4.0 (104)	4.5 (215)	4.4 (409)
	2	5.4 (16)	4.9 (27)	4.3 (46)	4.6 (89)
	3	11.8 (12)	4.5 (9)	3.7 (20)	4.9 (41)
	Total	4.0 (1,279)	3.2 (874)	3.4 (1,072)	3.6 (3,225)
Malformations of central nervous system*	0	1.0 (303)	0.6 (134)	0.7 (162)	0.8 (599)
	1	0.8 (15)	0.7 (17)	1.0 (46)	0.8 (78)
	2	1.7 (5)	1.6 (9)	1.3 (14)	1.5 (28)
	3	4.9 (5)	1.0 (2)	1.3 (7)	1.7 (14)
	Total	1.0 (328)	0.6 (162)	0.7 (229)	0.8 (719)
Malformations of heart and great vessels*	0	0.3 (96)	0.3 (80)	0.4 (105)	0.4 (281)
	1	0.5 (10)	0.4 (11)	0.8 (36)	0.6 (57)
	2	1.0 (3)	0.5 (3)	0.7 (7)	0.7 (13)
	3	2.9 (3)	1.0 (2)	0.9 (5)	1.2 (10)
	Total	0.4 (112)	0.4 (96)	0.5 (153)	0.4 (361)

* Rates are expressed per 100 related births; malformed infants are shown in parentheses

TABLE III
STILLBIRTHS AND INFANT DEATHS AMONG MALFORMED SINGLETON BIRTHS

Type of Malformation	No. of Malformed Infants	Cumulative Deaths			Mortality at 1 year as percent of All Cases
		Stillborn	At 1 week	At 1 year	
Central nervous system					
Anencephaly	281	260	281	281	100
Spina bifida (without anencephaly)	331	72	126	194	59
Hydrocephaly (alone)	82	44	49	57	70
Other defects	49	9	9	21	43
Total	743	385	465	553	74
Heart and great vessels					
Patent ductus	38	0	11	16	42
Septal defects (alone)	73	5	16	30	41
Transposition of great vessels	34	0	1	24	71
Coarctation of aorta	30	1	12	30	100
Fallot's tetrad	16	0	2	8	50
Other specified defects	90	1	24	53	59
Unspecified defects	117	1	10	27	23
Total	398	8	76	188	47
Alimentary system					
Cleft lip and/or palate	187	11	19	21	11
Pyloric stenosis	196	0	0	4	2
Atresia—oesophageal	37	0	6	14	38
—intestinal	21	1	4	7	33
—anorectal	37	0	8	15	41
Other systems					
Talipes	311	7	10	14	5
Hypospadias	113	0	2	4	4
Other urogenital	129	8	33	48	37
Down's syndrome	90	5	14	30	33

RESULTS

ABORTIONS AMONG EARLIER PREGNANCIES

The analysis has been confined to singleton births, of which there were 90,921 in the three years of the investigation. Data regarding a history of previous abortion are complete for 90,202 births. Of the 134,289 earlier pregnancies recorded in these women, 15,639 (11.6%) terminated in abortion. Congenital malformations were reported in 3,242 singleton infants and data on previous abortions are complete for 3,225 of them.

In Table I, the incidence of abortion among previous pregnancies (for each type of malformation) is compared with the rate recorded for all births (11.6%). Abortion rates were significantly raised in malformations of the central nervous system and of the heart and great vessels. Several individual malformations also had increased rates, viz., anencephaly, spina bifida, patent ductus, septal defects, dislocation of hip, talipes, and urogenital defects (excluding hypospadias). In pyloric stenosis the rate was significantly lower than expected.

Table II shows how the incidence of all malformations combined varied with maternal parity and with the number of previous abortions. Malformation incidence was lowest (at all parities) in the absence of a previous history of abortion. In primiparous births, incidence rose with increase in the number of previous abortions, being particularly high (11.8%) after three abortions. There was a similar pattern in malformations of the central nervous system and of the heart and great vessels.

STILLBIRTHS AND INFANT DEATHS

The cumulative mortality up to 1 year is shown in Table III.

MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM
There were 743 infants with defects of the central nervous system; 281 had anencephaly with or without spina bifida, and 331 had spina bifida without anencephaly.

Anencephaly Ninety-three per cent of anencephalics were stillborn and mortality was complete within four days of birth.

Spina bifida (excluding anencephaly and encephalocoele) Twenty-two per cent were stillborn and mortality had reached 59% by the first anniversary of birth.

Some of the important determinants of spina bifida mortality are examined in Table IV. It was higher in females (64%) than in males (51%). At birth weights below 4 lb. no infants survived; between 4 lb and 5 lb 15 oz the mortality rate (63%) was appreciably greater than at higher weights (51%).

An associated hydrocephalus increased the mortality from 39% to 76%. Mortality varied

TABLE IV
MORTALITY IN SPINA BIFIDA
(EXCLUDING ANENCEPHALY AND ENCEPHALOCOELE)

Factors Examined	No. of Malformed Infants	Cumulative Mortality		Mortality at 1 year as percent of All Cases
		Stillborn	At 1 year	
All cases ..	331	72	194	59
Male ..	142	29	73	51
Female ..	189	43	121	64
Birth weight				
Less than 4 lb ..	22	13	22	100
4 lb - ..	71	22	45	63
6 lb - ..	165	26	85	51
8 lb + ..	61	10	31	51
Not known ..	12	1	11	92
Associated hydrocephalus				
No ..	157	13	62	39
Yes ..	174	59	132	76
Social Class				
I and II ..	34	4	18	53
III ..	168	36	94	56
IV and V ..	118	27	74	63
Other or not known ..	11	5	8	73

according to social class, rising from 53% in social classes I and II to 63% in classes IV and V.

Other malformations Fifty-four per cent of cases of congenital primary hydrocephalus were stillborn and mortality by 1 year was 70%. Of 25 infants with encephalocoele, 8 were stillborn and 13 died in infancy; of 13 infants with microcephalus, one was stillborn and four died in infancy.

MALFORMATIONS OF THE HEART AND GREAT VESSELS Including cases of Down's syndrome, there were in the series 398 infants with cardiovascular defects, of whom 8 were stillborn, 68 died in the first week of life, and a further 112 died in the remainder of the first year. Mortality at 1 year was 47%.

Among specified defects, mortality ranged from 41% in septal defects (without other cardiovascular defects) to 100% in coarctation of the aorta. Mortality in unspecified defects was much lower (23%).

MALFORMATIONS OF THE ALIMENTARY SYSTEM Mortality in infants with clefts of the lip and/or palate was 11% and with pyloric stenosis 2%. Of the 37 infants with oesophageal atresia 14 died in infancy, 8 of the deaths being in infants with an associated cardiac malformation. Intestinal atresia had a similar mortality; of 21 cases, one was stillborn and six died in infancy, one death being associated with a cardiac malformation. Of the 37 infants with anorectal atresia 15 died in infancy, four being associated with a cardiac defect.

MISCELLANEOUS MALFORMATIONS Mortality among 311 infants with talipes (not associated with spina bifida) was 5%. There was also low mortality in hypospadias (4%) although a much higher rate in other urogenital defects (37%), 16 of the 48 deaths being in infants with associated malformations (congenital heart disease or intestinal atresia).

TABLE V
MORTALITY IN DOWN'S SYNDROME

Factors Examined	No. of Malformed Infants	Cumulative Mortality		Mortality at 1 year as percent of All Cases
		Stillborn	At 1 year	
All cases ..	90	5	30	33
Male ..	38	0	13	34
Female ..	52	5	17	33
Birth weight				
Less than 4 lb...	6	1	3	50
4 lb— ..	30	0	10	33
6 lb— ..	44	4	15	34
8 lb+ ..	8	0	2	25
Not known ..	2	0	0	0
Associated congenital heart disease				
No ..	63	3	17	27
Yes ..	27	2	13	48

Of 90 infants with Down's syndrome, 5 were stillborn and 25 died in infancy, the cumulative mortality at 1 year being 33%. There was no sex difference in mortality but low birth weight appears to have an important influence on mortality (Table V). At weights under 4 lb mortality was 50% but decreased to 25% at weights of 8 lb and over. Mortality was high (48%) in cases with a reported cardiac defect, although it is possible that here, as with other malformations, the existence of the associated defect was discovered (or reported) only as a result of necropsy examination.

DISCUSSION

The prevalence of malformations at birth depends on (1) the incidence at conception, and (2) the loss of malformed embryos or fetuses early in pregnancy (before the 28th week). For this reason, a history of previous abortions in relation to the prevalence at birth of malformation is of great interest. Raised abortion rates have been recorded for mothers of children with malformations of the central nervous system (Malpas, 1937; Böök and Rayner, 1950; Record and McKeown, 1950; Smithells, Chinn and Franklin, 1964; Smithells and Chinn, 1965; Richards, McIntosh, and Sweeney, 1972). Although these reports are based on retrospective enquiries (with the well-recognized bias that women who have given birth to malformed infants are more likely to

remember and report previous abortions than women who have normal infants), they are very suggestive of increased fetal loss in these families. In the present study, total malformations of the central nervous system and cardiovascular system were associated with a raised abortion rate among previous pregnancies, as were several individual malformations; malformation prevalence at birth was found to rise with an increase in the number of previous abortions.

A very high frequency of malformations is found among spontaneously aborted fetuses (Warburton and Fraser, 1959; Hayashi, 1961) and there is evidence that a high proportion of malformed fetuses are lost by spontaneous abortion (Nishimura, 1970). For several malformations, there is an increased risk of recurrence after the birth of an affected child (Blyth and Carter, 1969) and Richards, McIntosh, and Sweeney (1972) found that in mothers giving birth to infants with anencephaly or spina bifida, 41% of all known pregnancies ended in either abortion or the birth of a child with a congenital defect.

Having found asymmetries in family structure for Down's syndrome, congenital heart disease, pyloric stenosis, and oral clefts, Knox (1963) suggested that the determinants of many malformations are associated with lethal effects affecting family fertility, in many instances sex-biased, and that in all likelihood 'failure to be born is at least as frequent a manifestation of these determinants as is the malformation itself'. It seems reasonable to postulate that in the present study much of the fetal loss among earlier pregnancies was due to malformation.

Congenital malformations are also an important cause of stillbirth and of death in infancy and early childhood. McKeown and Record (1960) found that only half of the malformed liveborn children in their Birmingham study were alive at age 5 compared with 95% of those not malformed. In the present series, mortality (by the first anniversary of birth) was greatest among infants with malformations of the central nervous system (74%), malformations of the heart and great vessels (47%), anorectal atresia (41%), and oesophageal atresia (38%).

Mortality in malformed infants is related to several factors:

(a) Sex of infant: For two malformations, higher death rates have been reported among females, viz., spina bifida (Doran and Guthkelch, 1961; Laurence and Tew, 1971; Wilson, 1970) and Down's syndrome (Penrose, 1932; Øster, 1953; Record and Smith, 1955; Carter, 1958; Cowie, 1970). In the present

study, mortality in spina bifida was highest among females, but there was no sex difference in mortality in Down's syndrome.

(b) Birth weight: Mortality in spina bifida and in Down's syndrome is closely related to birth weight in this series; a similar association has been reported by Cozzi and Wilkinson (1968) for anoctal anomalies.

(c) Associated defects: Mortality is considerably increased where there is more than one malformation present (McKeown and Record, 1960). This increased risk is seen in the present series when spina bifida is accompanied by hydrocephalus, Down's syndrome by congenital heart disease, alimentary tract atresia by congenital heart disease, and defects of the urogenital tract (excluding hypospadias) by congenital heart disease or intestinal atresia.

(d) Treatment: In this study no attempt was made to relate mortality and survival to the type of treatment given to the infant. However, it is known that surgical treatment of spina bifida and its complications was increasing during the survey years. The effect of improved care is seen in the fall in mortality since an earlier study in South Wales when the cumulative mortality at 1 year among spina bifida births in 1956-62 was 82% (Laurence and Tew, 1971).

SUMMARY

Using data from the South Wales Survey of Congenital Malformations, it was found that malformations of the central nervous system and the cardiovascular system were associated with significantly raised abortion rates among previous pregnancies, as also were several individual malformations. Malformation prevalence at birth was shown to rise with an increase in the number of previous abortions; this trend was very marked in primiparous births.

Cumulative mortality rates at the first anniversary of birth are presented and the disadvantageous effects of low birth weight and of the presence of associated defects are clearly illustrated.

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