

were then followed up. Seven of the eight patients who had a total cumulative dose of less than 450 mg/m² did not show a significant change.

Measurement of the STI is a sensitive means of detecting myocardial injury induced by DXR. It should be emphasised that changes in the STI may subside weeks or months after stopping the drug, even in patients who may have a very high total dose. These patients, however, remain at high risk of developing congestive heart failure if DXR is restarted, even up to two years after the last dose of the drug. We recommend, therefore, that a total dose of DXR of 550 mg/m² should not be exceeded unless the benefit of achieving further remission outweighs the risk of cardiotoxicity. Carefully monitoring cardiac function by measuring the STI in these circumstances will aid the early detection of myocardial dysfunction. Finally, as the recommended total dose of DXR is relatively low, the drug is probably best reserved for induction treatment in patients with AML. This is especially important if modern induction protocols using relatively high doses per course are used. Maintenance chemotherapy may be carried out using non-cardiotoxic agents known to be effective in this disease.

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Comparison of central nervous system malformations in spontaneous abortions in Northern Ireland and south-east England

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Summary and conclusions

A study of 1140 pregnancies ending in spontaneous abortion disclosed a central nervous system (CNS) malformation in 4.9% of all complete conceptuses. Life-table analysis suggested that the incidence of CNS malformations is 16/1000 at the beginning of the eighth week of gestation. It was also estimated that only one-fifth of these infants are born alive, 41% being aborted spontaneously and 38% stillborn.

A hypothesis that differences in the incidence of CNS malformations result from area differences in the mortality rate of malformed embryos and fetuses was examined by comparing the findings in Northern Ireland, an area of high incidence, with those in south-east England, an area of low incidence. In Northern Ireland 4.6% of complete conceptuses had a CNS malformation compared with 3.0% in south-east England, but the difference was not statistically significant.

There is no evidence that in Northern Ireland a lower mortality rate among malformed fetuses and embryos is responsible for the high incidence of malformation at birth. The geographical variation of CNS malformations in the United Kingdom still awaits explanation.

Introduction

In the United Kingdom the incidence of central nervous system (CNS) malformations shows a pronounced geographical gradient, which steadily increases from the south and east to the north and west; the incidence (per 1000 total births) in south-east England is 2.95,¹ in Wales 7.6,² and in Northern Ireland 8.6.³ This gradient has been confirmed by several other reliable studies. The ratio of the prevalence of spina bifida to anencephaly is relatively constant, with a slight excess of spina bifida. In a study of regional variation in incidence of these malformations at birth, Roberts and Lloyd⁴ found an inverse relation between previous spontaneous abortion rates and the prevalence at birth of CNS malformations. They hypothesised that there is little or no difference in the incidence of CNS defects shortly after conception and that the observed differences in the third trimester arise only because of a greater prenatal mortality rate among malformed embryos in areas of low incidence. This may be tested by examining spontaneously aborted fetuses from areas with high and low incidences of CNS malformations; if correct there should be a higher proportion of aborted conceptuses with CNS defects in the area of low incidence.⁵ In south-east England

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Creasy and Alberman⁶ found that 3.6% of complete fetuses or embryos or 3% of all complete conceptuses had a CNS malformation. We report the prevalence of CNS malformations in spontaneous abortions in an area of Northern Ireland, a region of high incidence, and compare the findings with those for south-east England, an area of low incidence.

Methods

For health and social service purposes Northern Ireland is divided into four areas. The survey was confined to the Eastern area, which comprises most of the hospitals in and around Belfast. Products of conception and curettings were collected from all women who had a spontaneous abortion between 1 October 1976 and 30 September 1977. Of these patients, 98% were interviewed by one of us (JCRMM) and in the remaining 2% details of the pregnancy were obtained from the hospital records. A total of 1140 pregnancies ended in spontaneous abortion: 1095 patients had one abortion, 21 had two, and one patient had three abortions. There were also 36 ectopic pregnancies. When identified, a fetus, embryo, or fetal parts were weighed, measured, photographed, and fixed in 10% formalin. A binocular dissecting microscope was used to examine small specimens. During the study period a total of 10 493 births occurred in the Eastern area.

TABLE I—Gestational age of fetuses and embryos with CNS malformation at time of expulsion

Type of defect	Gestational age (weeks)				Total
	<12	12-15	16-19	20-23	
Spina bifida		2	1		3
Encephalocele	5	1			6
Anencephaly		1		1	2
Hydrocephalus		1			1
Craniorachischisis	3	1			4
Total	8	6	1	1	16

TABLE II—Clinical details in cases of spontaneous abortion of fetuses and embryos with CNS malformation

Survey No	Type of defect	Crown-rump length (cm)	Duration of amenorrhoea (days)	Pregnancies before abortion	Outcome of immediate past pregnancy	Age of mother (years)	Family history of CNS malformation
0149	Craniorachischisis	1.4	71	1+0	LB	37	
0230	Encephalocele	0.4	81	0+1	SA	32	
0292	Hydrocephalus	2.0	94	1+0	LB	23	
0299	Encephalocele	0.2	95	5+0	LB	35	
0407	Craniorachischisis	0.3	29	2+0	LB	25	
0563	Spina bifida	1.3	94	4+1	LB	26	
0609	Encephalocele	1.9	70	4+1	LB	30	Husband's nephew with spina bifida
0648	Spina bifida	4.0	106	0+1	SA	30	
0782	Spina bifida	2.3	94	0+0		21	
0810	Encephalocele	2.2	81	3+0	SB (CNS)	29	Previous infant with anencephaly
0882	Encephalocele	0.5	74	0+0		26	
0957	Craniorachischisis	0.7	55	5+2	LB	30	Mother's sister's child with congenital hydrocephalus
1087	Anencephaly	10.0	144	0+0		18	
1122	Encephalocele	0.3	77	3+1	SA	41	
1166	Anencephaly	0.9	101	0+0		26	
1190	Craniorachischisis	1.1	93	3+1	LB	34	

LB = Livebirth. SA = Spontaneous abortion. SB = Stillbirth. CNS = Central nervous system malformation.

TABLE III—Estimated mortality table of cohort of conceptuses counted at week 8. (Figures in parentheses from Creasy and Alberman⁶)

Mode of spontaneous termination of pregnancy or expulsion of conceptus	No of complete specimens studied	Observed No with CNS malformation	Estimated prevalence of CNS malformation/1000 terminations of pregnancy	Estimated No of conceptuses (of cohort of 1000 counted at 8 weeks) expelled in way indicated*	Estimated No of conceptuses (of cohort) expelled with CNS malformation in way indicated	Estimated % of all CNS malformations in cohort expelled in way indicated
Aborted at:						
8-11 weeks	97	8	82.47 (21.6)	54.39 (69.90)	4.49 (1.51)	28.43 (28.6)
12-15 weeks	101	5	49.50 (22.2)	34.96 (41.65)	1.73 (0.92)	10.96 (17.4)
16-19 weeks	44	1	22.73 (20.2)	10.08 (11.83)	0.23 (0.24)	1.46 (4.5)
20-23 weeks	40	1	25.00 (8.4)	4.00 (7.42)	0.10 (0.06)	0.63 (1.1)
24-27 weeks	37	0	0 (36.7)	2.10 (2.74)	0 (0.10)	0 (1.9)
Stillborn after 27 weeks†	539	143	265.31 (105.2)	22.99 (11.26)	6.10 (1.18)	38.63 (22.3)
Live born†	40 264	145	3.60 (1.5)	871.48 (855.20)	3.14 (1.28)	19.89 (24.2)
Total				1000.00	15.79 (5.29)	100.00 (100.0)

*Data from Stevenson and Warnock.⁷

†Total stillbirths and live births for Eastern area, Northern Ireland, 1974-7.

Results

The 1140 abortions investigated included 270 complete fetuses and embryos and 56 intact empty sacs. Of the 326 complete specimens, 69 fetuses and embryos were abnormal; 36 (11.0%) were nodular stunted embryos, 16 (4.9%) had a CNS malformation, and 17 (5.2%) had other congenital abnormalities. Of the 16 fetuses and embryos with a CNS malformation (table I), six had an encephalocele; five of these were aborted before 12 weeks of gestation. Craniorachischisis also predominated among the earlier abortions, three of the four such abortuses being under 12 weeks of gestation. Spina bifida and anencephaly were more prevalent among fetuses aborted later in pregnancy, five of the eight fetuses aborted between 12 and 23 weeks of gestation having spina bifida or anencephaly.

Table II summarises the clinical details in the 16 cases of CNS malformation. The women had a total of 39 pregnancies; 8 (20.5%) had ended in a previous spontaneous abortion, and among the 31 previous births there was one case of anencephaly. Four mothers were primigravidae. Among the other 12 mothers the immediate past pregnancy had resulted in a live birth in eight cases, spontaneous abortion in three, and an anencephalic stillbirth in one.

The prevalence of CNS malformations in abortuses, omitting the isolated case of hydrocephalus and calculated as a fraction of all complete specimens, was 4.6%. To permit comparison of figures for abortions with those for stillbirths and live births a life table similar to that of Creasy and Alberman⁶ was constructed using a pregnancy study in Belfast in 1957,⁷ the total stillbirths and live births in the Eastern area of Northern Ireland for 1974-7 inclusive, and all complete fetuses in the survey aborted between 8 and 27 weeks of gestation. The proportion of affected conceptuses lost during each four-week period of gestation was estimated, in each case from the proportion with a CNS malformation in the present survey among the pregnancies at risk, as given by the life table (table III).

The calculations showed that the prevalence of abortuses with a CNS malformation decreased steadily from 82.47/1000 in the 8-11-week period to 25.00/1000 in the 20-23-week period. The overall rate of CNS malformations among spontaneous abortions was estimated at about 36/1000. This was one-seventh of that among stillbirths (265/1000) but 10 times the rate among live births in the same

area (3.60/1000). At the beginning of the eighth week of gestation almost 16/1000 of all conceptuses have a CNS malformation; 80% of these, however, fail to be born alive, about half of this mortality occurring as spontaneous abortions.

The hypothesis that the incidence of CNS malformations is uniform at conception with differences in area prevalence resulting from area differences in the mortality of malformed embryos and fetuses⁴ may be tested by comparing the findings of the present study in an area of high incidence with those for south-east England, an area of low incidence.⁶ In Northern Ireland the proportion of complete abortion specimens with CNS malformations was 4.6%, and in south-east England 3.0%. The relative risk for each area was estimated according to the method of Woolf⁸; the difference in the relative risk of CNS malformations among spontaneous abortions from both areas was not significant ($\chi^2=1.26$; DF=1; $0.3 > P > 0.2$).

Discussion

Fetuses with CNS malformations, the most common congenital defect found at birth in the UK, are relatively common in spontaneous abortions, ranging from 3% to 7%.^{6, 9, 10} In our series 16 out of 326 (4.9%) complete conceptuses aborted spontaneously had a CNS malformation. Using a life-table method, we estimated the overall rate of CNS malformations among spontaneous abortions to be about 36/1000, which is 10 times the rate among live births. Some 80% of conceptuses with a CNS malformation fail to be born alive. These findings are similar to those from south-east England. At the beginning of the eighth week of gestation about 16/1000 conceptuses had a CNS malformation, which is three times higher than in south-east England.

Our results in an area with a high incidence of CNS malformations compared with those from south-east England, an area of low incidence,⁶ do not support the hypothesis⁴ that the geographical variation in the incidences of CNS malformations is due to area differences in the mortality rate of malformed embryos and fetuses. Fedrick and Adelstein,¹¹ using data from

the 1958 British Perinatal Mortality Survey, found evidence that the history of preceding abortions among all mothers was slightly more prevalent in areas where the rates of stillbirth and neonatal death with CNS malformations were low, but the order of magnitude was much less than in the study of Roberts and Lloyd.⁴ Our findings suggest that in an area of high incidence of CNS malformations the number of malformed fetuses lost by spontaneous abortion is as high as in areas with a low incidence. The striking geographical variation in the incidence of CNS malformations in the United Kingdom still awaits explanation.

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ONE HUNDRED YEARS AGO "Emily Hulbert, aged 18, attended as an out-patient at St Mary's Hospital on March 24th, with signs of an abscess on the right elbow. She applied again on March 31st, with a distinct abscess on the outside of the elbow, and a small black spot over the left eye, which she had knocked three days before. She stated that she was living over stables where glandered horses were lying, and also that her sister, aged fifteen months, had died two days previously of the same disease. The face was puffy, especially the eyelids; the left eyelid was swollen; over the eye was a darkened patch; the epidermis was raised in bullæ. Temperature 103 deg. She was perfectly conscious and in no pain, but rather sleepy. The bowels were open. She was placed in a ward well ventilated, and ordered one drachm of tincture of perchloride of iron every three hours. On April 1st, temperature 104.2 deg.; pulse 110. She was still very drowsy, but answered questions readily; the places on the forehead had commenced to slough. April 2nd. Temperature 103.2 deg.; pulse 120. She was much the same. April 4th. Free incisions were made in the slough on the forehead, which was three inches in diameter; the elbow looked quite healthy; the left eye was completely closed. Temperature 103.6 deg.; pulse 128. April 6th. She had now become delirious, but was conscious when spoken to in a loud tone of voice. April 7th. The right ala of the nose had now become black and gangrenous, and with it there was a sanious discharge from the nostril. Temperature 103.8 deg.; pulse 136. April 8th. The wound had extended to the scalp. The left ankle and left wrist were swollen and tender; pustules had formed on the shoulder, knee, and foot of the right side. There were muttering delirium and incontinence of urine and fæces. Temperature 104.8 deg.; pulse 160. April 9th. The slough on the forehead came away and a healthy granulating surface was left, with the bone exposed in two small places. She was very feeble; the pulse was very quick. She appeared to be rapidly sinking, and died at 6 p.m. At the necropsy, all the organs were found much congested. There was nothing else abnormal. No abscesses were found in the internal organs. The infection evidently came from the wound in the forehead, as the elbow

remained healthy to the last, although slow to set up repair. The pustules on the body commended as papules, which became inflamed, with a hard base; in twenty-four hours, they became pustular and soon turned black and hard, and rapidly spread."

An inquest on the case was held by Dr Hardwicke, on the 12th instant, at which it was proved that the deceased had resided over mews in which several horses had been suffering from glanders. An infant child died just before the deceased went into hospital, from farcy and glanders. Dr Dudfield, medical officer of health for Kensington parish, said he had inspected the premises, and found one horse suffering from farcy and two from glanders. The place was in a very bad condition, and, when the stable door was shut, all the foul air must go up into the rooms occupied by this family. No notices had been given either to the Privy Council, the Metropolitan Board of Works, or the police, as required by the Contagious Diseases Act. The inquest was adjourned until the 17th, when the jury returned a verdict that Hulbert died from the effects of glanders. They were of opinion that the provisions of the Contagious Diseases (Animals) Act of 1878, with reference to the outbreak of glanders and to the treatment and disposal of the carcasses of horses suffering from such diseases, had not been duly carried out, and they desired that the facts given in evidence should be brought before the Privy Council, and steps taken to avoid, if possible, the occurrence of such accidents in future.

The cab proprietor, at whose stables the girl resided, was on Monday last, charged before the magistrate of the Hammersmith Police Court, on a summons for an infringement of the Contagious Diseases (Animals) Act and an Order of Her Majesty's Privy Council known as "Animal Order of 1878." There were two summonses, one for not giving notice to the police of a glandered horse in his possession, and the second for not giving notice of another suffering from "farcy." As the proper precautions were disregarded, the deaths of two persons from glanders had resulted. The defendant was fined the full penalty of £20 in each case, with one guinea costs. (*British Medical Journal*, 1879.)