

# Neural tube defects, maternal cohorts, and age: a pointer to aetiology

J P Bound, B J Francis, P W Harvey

## Abstract

The effects of maternal year of birth and age on the declining prevalence of neural tube defects after 1972-3 were examined using 403 cases ascertained in a prospective study in the Fylde of Lancashire during 1957-89. Matched case-control data were analysed using conditional logistic regression analysis.

The risk of an anencephalic baby was significantly greater for older mothers, but changes in the maternal age distribution in the population did not appear to be relevant to the recent decline in prevalence. Antenatal diagnosis and termination of pregnancy was the major cause.

Mothers born before 1950 were at significantly greater risk of producing a baby with spina bifida or cranium bifidum. We suggest that abandonment of mercury as a therapeutic agent for infants in the early 1950s is a possible factor in the current decline of these malformations.

This paper examines the relationship between year of maternal birth, maternal age, and the prevalence of neural tube defects in the Fylde of Lancashire, with particular reference to the decline after 1972-3.

Janerich showed by cohort analysis that the absolute risk of anencephaly was more directly related to the mother's year of birth than to that of the affected child.<sup>1</sup> This suggested that environmental aetiological factors act early in the mother's life affecting the risk of anencephalic offspring throughout her reproductive period.

In the Fylde during 1957-76 the prevalence of anencephaly fell suddenly and significantly after 1968.<sup>2</sup> The prevalence of spina bifida and cranium bifidum also fell, but to a lesser extent. Subsequently, after the early 1970s, both types of neural tube defect declined.

In England and Wales the decline in prevalence of neural tube defects that began in 1972 was not explicable solely by prenatal diagnosis and termination of pregnancy.<sup>3</sup> In Liverpool the decline from 1974 was more noticeable for anencephaly than spina bifida.<sup>4</sup> In Sheffield a dramatic decline in spina bifida births was partly due to antenatal diagnosis and termination, which was even more successful in reducing anencephaly.<sup>5</sup>

We have sought to explain the underlying decline by looking for a maternal age or cohort effect and, if found, a cause.

## Methods

Cases of neural tube defect were ascertained as part of a prospective survey, described in detail

previously, of babies with major congenital malformations born in the Fylde to residents there during 1957-81.<sup>6</sup> Data was collected daily by one paediatrician and a very high rate of necropsies was maintained. Recording of cases was continued until the end of 1989. Terminations of pregnancy for antenatal diagnosis of neural tube defects were ascertained from the local obstetricians' records.

The total numbers of cases, including terminations, were 190 for anencephaly, 181 for spina bifida cystica, and 32 for cranium bifidum cysticum (excluding five early cases where the mother's date of birth was not known). There were 116 282 live births and stillbirths in the 33 years (1957-89).

The separation of the effects of maternal age at birth of child, year of birth of the child (or termination of the pregnancy), and year of birth of the mother cannot be achieved using a standard study design, as the date of birth of the child (BC) is mathematically defined by the date of birth of the mother (BM) and the age of the mother (AM) through the relation  $BC = BM + AM$ . The statistical problem in separating the (maternal) age, (birth) period, and (maternal) cohort effects has been discussed by many authors.<sup>7-8</sup> Plewis makes the point that it is always possible to design a study to estimate any two of these three effects, and gives several study designs.<sup>9</sup>

In this study, we have adopted a matched case-control approach; by controlling for year of birth of the child then the effects of maternal age and maternal year of birth may be separated by suitable statistical techniques. This procedure allows us to seek an explanation for a known temporal effect (the decrease in the rates of anencephaly and of spina bifida and cranium bifidum after the early 1970s).

Controls were obtained from birth records of the consultant obstetric hospital, which served all the Fylde. It was possible, therefore, to match cases born outside the hospital with controls from the same district. A single control was used for each case, taking the first birth of a normal baby for the same year and month which matched for district of residence of the mother and sex of the baby. The date of birth and parity of the control mother was then recorded.

The statistical analysis of matched case-control data using conditional logistic regression analysis is described in Breslow and Day.<sup>10</sup> The statistical package GLIM is well suited to fit such models and Adena and Wilson describe a range of procedures.<sup>11-12</sup> We used their procedures, but included the full set of nuisance parameters in the linear model<sup>13</sup> giving us greater accuracy. Maternal age and

Department of  
Paediatrics,  
Victoria Hospital,  
Blackpool FY3 8NR  
J P Bound

Centre for Applied  
Statistics,  
Lancaster University  
B J Francis

Department of  
Pathology,  
Royal Lancaster  
Infirmary  
P W Harvey

Correspondence to:  
Dr Bound.

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maternal year of birth were treated as categorical variables.

We adopted a backward elimination procedure for determining a suitable model; firstly by including all risk factors of interest—maternal age, maternal year of birth, and parity—in the initial model and then at each stage excluding the most unimportant variable, using the deviance (likelihood ratio statistic) as a criterion for comparing nested models.<sup>13</sup> The procedure terminated when all remaining risk factors were significant. In this way the competing effects of maternal age and maternal year of birth could be assessed.

Separate analyses were carried out for anencephaly and for spina bifida and cranium bifidum. For each analysis, we provide a table of relative risk factors for the final model with 95% confidence intervals. For maternal age, the risks are relative to the youngest age group, and for maternal year of birth, the risks are relative to the earliest maternal birth cohort.

## Results

After 1972 anencephalic births in the Fylde declined to zero (tables 1 and 2). Much of this fall was due to antenatal diagnosis of anencephaly with termination of pregnancy. Births of babies with spina bifida and cranium bifidum also declined after 1973 but the fall was less than for anencephaly. However there were fewer terminations for spina bifida and cranium bifidum so that the underlying decline in prevalence was greater than for anencephaly.

### ANENCEPHALY

Parity (changes in deviance=0.36 on 1 df;  $p=0.55$ ) followed by maternal year of birth (change in deviance=1.84 on 3 df;  $p=0.61$ ) were found to be unimportant and were excluded from the logistic regression model. A strong effect of maternal age was observed which could not be excluded from the model (change in deviance=17.66 on 2 df;  $p<0.0001$ ).

Table 1 Prevalence of neural tube defects in the Fylde of Lancashire 1957–89

Period	Total births	Anencephaly		Spina bifida and cranium bifidum	
		Births	Prevalence/1000 births	Births	Prevalence/1000 births
1957–61	18321	59	3.2	57	3.1
1962–66	20827	53	2.5	58	2.8
1967–71	19132	24	1.3	40	2.1
1972–76	15281	20	1.3	31	2.0
1977–81	14888	9	0.6	11	0.7
1982–86	16488	2	0.1	7	0.4
1987–89	11345	0	0.0	3	0.3

Table 2 Prevalence from 1977 including terminations of pregnancy for antenatal diagnosis of neural tube defects

Period	Total births	Anencephaly		Spina bifida and cranium bifidum	
		Births	Prevalence/1000 births	Births	Prevalence/1000 births
1977–81	14888	13	0.9	11	0.7
1982–86	16488	12	0.7	13	0.8
1987–89	11345	9	0.8	8	0.7

Table 3 Maternal age and relative risk for anencephaly

	Relative risk	95% Confidence interval
Maternal age:		
25–29 v <25	1.921	1.134 to 3.251
≥30 v <25	2.910	1.704 to 4.967

Table 4 Maternal year of birth and relative risk for spina bifida and cranium bifidum

	Relative risk	95% Confidence interval
Maternal year of birth:		
1940–1949 v pre-1940	0.9336	0.548 to 1.590
1950–1959 v pre-1940	0.2574	0.085 to 0.783
Post 1959 v pre-1940	0.2845	0.068 to 1.191

The relative risk for mothers over 25 is nearly double that for younger mothers (table 3), and the relative risk increases still further for mothers over 30, being nearly treble that of younger mothers.

### SPINA BIFIDA AND CRANIUM BIFIDUM

Parity was again the least important variable (change in deviance=0.04 on 1 df;  $p=0.84$ ) but maternal age (change in deviance=1.15 on 2 df;  $p=0.56$ ) was also found to be unimportant and was excluded from the model, leaving maternal year of birth as the only important factor (change in deviance=7.90 on 3 df;  $p<0.05$ ). Replacing the maternal year of birth factor by a linear trend for maternal year of birth produced a significant change of deviance of 5.99 on 2 df ( $p=0.05$ ) and the linear trend was no longer significant (change in deviance=1.91 on 1 df;  $p=0.17$ ).

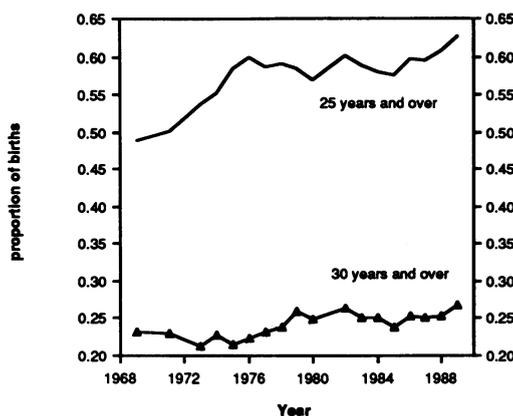
It can be seen from table 4 that maternal year of birth is a significant risk factor. The relative risk is close to one until 1950, then declines substantially. For mothers born before 1950, the risk of spina bifida or cranium bifidum is more than treble that for mothers born after 1950.

## Discussion

The sudden significant fall in the prevalence of anencephaly in the Fylde after 1968 was not seen in north west England or nationally. It was associated with increasing hardness of the summer water in a supply which was confined to the Fylde.<sup>2</sup> The prevalence of spina bifida and cranium bifidum showed a small fall that was not significant.

After 1972–3 the prevalence of both anencephaly and spina bifida and cranium bifidum in the Fylde declined again, reflecting the trend in England and Wales.<sup>3</sup> Further, antenatal diagnosis of a neural tube defect with termination of the pregnancy, which was more successful in reducing anencephaly, could explain only part of the decline in prevalence, especially of spina bifida as was found in Sheffield.<sup>5</sup> Therefore our trends since 1972 are in accord with those found elsewhere and the results of the cohort studies should have general relevance.

The idea that environmental factors acting during the mother's early life could predispose her to produce babies with neural tube defects



Proportion of births in Fylde for two maternal age groups. Proportions based on hospital births up to 1980 and on all births from 1980.

later is not new. It has been suggested that non-specific interference with early growth and development may affect the reproductive and/or endocrine systems and contribute to the later production of neural tube defects.<sup>14</sup> The interference could be short or long lived and produced by many conditions, such as nutritional deficiencies, severe illness, or socio-cultural factors. Recently, a related idea has been proposed that environmental programming in fetal and infant life affects adult degenerative disease.<sup>15</sup>

#### ANENCEPHALY

We have found that the mother's year of birth did not affect her risk of having a baby with anencephaly. Her age did, the risk increasing in older mothers. However, apart from a slight dip in the proportion of mothers aged 30 years or more between 1971 and 1977, seen both in the Fylde (figure) and nationally, the proportion of older mothers increased up to 1989. Therefore the declining prevalence of anencephaly was unlikely to be due to change in maternal age distribution.

#### SPINA BIFIDA AND CRANIUM BIFIDUM

Maternal year of birth was an important risk factor. The evidence is that the decline in risk was sudden rather than gradual, with mothers born after 1949 significantly less likely to have an affected baby. In other words, fewer mothers could be regarded as preconditioned to have a baby with these anomalies. This is chronologically compatible with the fewer recorded births of affected babies after 1973 and suggests that, apart from termination, the underlying cause of the decline is to be sought in events in the early 1950s.

Janerich suggested that the 1918-9 influenza pandemic may have been a preconditioning event for the epidemic of neural tube defects which peaked in 1929-32.<sup>16</sup> However it is not possible to relate the current decline in spina bifida to the pattern of influenza infections. For example, if the pandemics of 1957 and 1969 were preconditioning events, an increased

prevalence of spina bifida would have been expected at a time when, in fact, it was in a prolonged decline.

Dietary deficiencies have also been suggested for preconditioning events. The most noticeable general improvement in nutrition occurred in 1940 with rationing and the provision of welfare foods for mothers and children.<sup>17</sup> This led to an immediate steep fall in perinatal mortality and improved growth of children, but we find little change in the risk to future mothers of a baby with spina bifida. The significant change occurred some 10 years later and we are unaware of any further relevant improvement in diet then.

Searching for other possible preconditioning events we noted that mercury was largely abandoned in the treatment of infants in the early 1950s. From 1948 warnings were given that the metal could cause pink disease in susceptible infants.<sup>18 19</sup> Mercury nephrosis was also described.<sup>20</sup> Apart from doctors' prescriptions of grey powder (mercury with chalk) or calomel for constipation and other symptoms in infants, calomel was a constituent of many proprietary teething powders which were widely used. For example, it was found that approximately 40% of the infant population of Manchester and Salford, and also of Warwickshire, received them.<sup>19</sup> Absorption of the metal could also occur from the use of mercurial ointments for treating napkin rashes. By 1955 a decline in pink disease and less mercury ingestion in infants was reported from Sheffield.<sup>21</sup> It became clear that mercury had caused a prolonged, serious, sometimes fatal illness in some infants. In addition, abortive cases had been common.<sup>22</sup> Anorexia was a prominent feature and mercury could have exerted its effect on subsequent reproduction through a period of malnutrition. Additionally, mercurial toxicity could have been specific as it has been reported to affect the germ cells of mammals.<sup>23</sup>

We suggest that administration of mercury was a possible preconditioning event for subsequent spina bifida or cranium bifidum and should be borne in mind when studying their aetiology, although it may now be difficult to obtain additional evidence to support the chronological findings.

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### Tuberculous hydrocephalus

As I was saying (1991;66:151), hydrocephalus occurs in a large majority of children with severe tuberculous meningitis. The best way of treating this hydrocephalus is uncertain and a report from South Africa compares several possible treatments (J Schoeman and colleagues, *Developmental Medicine and Child Neurology* 1991;33: 396-405). The study included 81 children aged 5 months to 8 years with severe tuberculous meningitis of MRC stages II and III at admission. (Stage I, early, mainly non-specific symptoms, little or no clinical sign of meningitis, no pareses, general condition good, fully conscious. Stage II, intermediate between I and III. Stage III advanced, extremely ill, deeply stuporose or comatose or with gross pareses.<sup>1</sup>) All the children received antituberculous treatment with four drugs; isoniazid, rifampicin, ethionamide, and pyrazinamide. Communicating hydrocephalus was present in 63 and non-communicating in 18. Those with non-communicating hydrocephalus were all treated early with a ventriculoperitoneal shunt. Those with communicating hydrocephalus were allocated randomly to one of four treatment groups: group A, no extra treatment (n=19), group B, weekly intrathecal hyaluronidase (n=19), group C, oral acetazolamide and frusemide (n=19), and group D, shunt surgery. Group D was discontinued after six patients had been operated upon because the authors considered the results of medical treatment to be 'encouraging'.

The lumbar cerebrospinal fluid pressure fell to normal over the first month in 41% of surviving patients in group A, 71% in group B, and 78% in group C, but mortality and morbidity were high in all groups and unaffected by the type of treatment. The overall mortality was 8% for stage II disease and 30% for stage III. Of the survivors of stage III disease 66% were severely mentally impaired (IQ<50), 27% were moderately mentally impaired (IQ 50-85), and 71% had a quadriplegia or a hemiplegia. Of stage II disease survivors 14% were severely mentally impaired, 69% moderately mentally impaired, and 26% had quadriplegia or hemiplegia.

The severity of disease at presentation is the most important factor determining outcome. This work has not shown that treatment of the hydrocephalus does anything to help these children. Intrathecal hyaluronidase did not seem to have harmful effects but acetazolamide and frusemide produced dehydration in three patients possibly associated with sagittal sinus thrombosis in one. Of the 24 children who had a ventriculoperitoneal shunt procedure five developed shunt dysfunction. Four of these had an infected shunt and they all died. These authors give no compelling reason for treating communicating hydrocephalus in tuberculous meningitis, although they advocate treatment with acetazolamide and frusemide. For non-communicating hydrocephalus they recommend early shunt surgery but the data they present do not permit an evaluation of that recommendation.

ARCHIVIST

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