

PAPERS AND ORIGINALS

Malignant Disease in Children whose Mothers had Chickenpox, Mumps, or Rubella in Pregnancy

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Summary

To test the hypothesis that leukaemia may follow virus infection in pregnancy an analysis was made of deaths which occurred in a cohort of children born in 1951 and 1952 after pregnancies in which the mothers suffered virus infections—chickenpox or mumps at any stage of gestation or rubella in the first 18 weeks. All deaths which occurred between the children's second birthday and the end of 1971 were studied.

Two deaths from leukaemia occurred among the children whose mothers suffered from chickenpox, a significant excess. There were no deaths from leukaemia among the other children, but the causes of the two deaths after maternal mumps—Ewing's tumour and Still's disease—are noted because of their rarity.

Introduction

There is growing interest in associations between events in pregnancy and the subsequent health of the child. The possibility that malignant disease in the child might follow maternal virus infection was suggested by Stewart *et al.* (1958). Since then there has been much experimental and epidemiological work relating virus infections to certain cancers, particularly leukaemia and Hodgkin's disease (Fedrick and Alberman, 1972). We therefore decided to investigate deaths among children whose mothers had, between 1950 and 1952, been notified to Medical Officers of Health as suffering from chickenpox, mumps, or rubella in pregnancy. The method of study was longitudinal; records were used showing whether the children had died or were alive at the end of 1971.

Method

Between 1950 and 1952 the Ministry of Health and the General Register Office collaborated with the Society of Medical

Officers of Health in a study of the teratogenic effects of virus infections in pregnancy (Manson *et al.*, 1960). Medical Officers of Health were responsible for the collection of information in their areas and made what arrangements were necessary. They enlisted the co-operation of general practitioners and the obstetric staffs of maternity hospitals, so that women who were receiving antenatal supervision from their family doctors and at hospital antenatal clinics, as well as those attending local health authority clinics, were under review—in fact most pregnant women in the country. From these women two groups of cases were selected: virus infection cases, and controls.

Doctors and midwives questioned the antenatal patients at the first and subsequent examinations as to the occurrence of any illness before or between visits. When a virus infection was reported the date of infection was ascertained, and if a doctor had been consulted he was asked for confirmation of the diagnosis and whether the infection was mild, moderate, or severe. The information was entered on the mother's record card and the Medical Officer of Health at the same time sent a registration card to the General Register Office.

After selection, virus and control cases were kept under observation until the termination of the pregnancy. In the event of abortion, miscarriage, or stillbirth the record card was completed as far as possible and returned to the General Register Office. In the case of live births the children were kept under observation for two years, medical examinations being undertaken as soon after birth as possible, at 1 year, and at 2 years of age by local health authority or hospital medical officers or by the family doctor.

Some of the records had been destroyed after the study was completed, but in 1972 there remained 272 relating to maternal chickenpox, 435 to maternal mumps, and 309 to maternal rubella for children who had survived to age 2; the chickenpox and mumps infections related to all stages of gestation, but the rubella infections were in the first 18 weeks only. For brevity we refer to these children as chickenpox, mumps, and rubella index cases respectively. To determine which had died subsequently—that is, between age 2 and 19 years—we used the National Health Service Central Registers, which function as clearing-houses for general practitioners' lists, and record the dates and places of deaths as they occur. All but 10 of the infants were identified from these registers; four had been adopted, three records were too incomplete to permit identification, and the last three could not be traced apparently because of

clerical errors in the study records. The causes of all deaths were then established from death certificates, and related hospital records examined. The records of antenatal care of these cases were traced from places of birth shown on birth registers. Executive Councils were also approached for access to general practitioner records of the deceased infants, but all of these had been destroyed.

Results

Two deaths, both from acute leukaemia, were traced among 270 chickenpox index cases successfully identified. Two other deaths, from Still's disease and from Ewing's tumour, were traced from 433 mumps index cases. Three deaths, one accidental, one from congenital heart disease, and one from asthma, were traced from 303 rubella index cases. Summaries of the medical histories of the dead children are given in the following case reports.

Case Reports

Case 1.—An 18-year-old primigravida developed chickenpox in the 23rd week of pregnancy. The infection was described as moderate in the notification to the medical officer of health. The obstetric case notes are scanty, but do record this episode, and state that this was the mother's second attack of chickenpox. No other abnormalities are recorded, and the patient gave birth to a daughter weighing 3,854 g at 40 weeks. The child was admitted to hospital at age 4½ with acute leukaemia. The notes from this admission record the mother's illness in pregnancy, and that the child had suffered measles at 13 months and pertussis at 4 years, but that development had otherwise been normal. She was treated with prednisolone and mercaptopurine with a good remission, remaining well until she developed chickenpox a year later. A few weeks after this she suffered a relapse, which was treated with methotrexate, and a four-month remission followed. She died after two months' further illness. The death certificate diagnosis was acute leukaemia.

Case 2.—A 21-year-old primigravida developed chickenpox in the 25th week of pregnancy, the infection being described as severe in the notification to the medical officer of health. The obstetric notes record this episode. Apart from a throat infection (α -haemolytic streptococci were isolated) at 34 weeks the pregnancy was otherwise normal, and the patient was delivered of a daughter weighing 3,656 g at 42 weeks' gestation. The child's development is not recorded, but the history from her first hospital admission states that she had bronchopneumonia at age 1 and frequent attacks of bronchitis. She presented with acute lymphatic leukaemia at age 3 and was treated with steroids and antimetabolites but with only a brief remission, dying in relapse two months after the start of her illness. The hospital record does not mention any maternal illnesses in pregnancy. The death certificate diagnosis was acute lymphoblastic leukaemia.

Case 3.—A 20-year-old primigravida developed mumps when five weeks pregnant, the infection being described as moderate. The obstetric notes (the patient did not present at hospital until much later) record this event. Apart from hypertension in the last two weeks the pregnancy was otherwise normal, and the patient was delivered of a son weighing 3,358 g at term. The child was first admitted to hospital shortly before he was 2 years old. The case notes from this admission have been lost, but from a discharge letter it seems he was admitted with fever and failure to thrive. No diagnosis was made. He was readmitted nine months later with signs suggestive of pneumonia. The discharge letter (again all that is available) records that this diagnosis was soon abandoned in favour of Still's disease on account of the temperature chart, high sedimentation rate, serum protein changes, splenomegaly, enlarged lymph nodes, and rash. He was treated with steroids, and his condition improved sufficiently to allow transfer to a convalescent hospital. During his nine months' stay there he suffered several respiratory and ear infections, all controlled with antibiotics, and he had other episodes of high fever (spiking chart) without localizing signs. After a period of relatively good health he developed high fever, vomiting, and diarrhoea, dying the same day. Necropsy showed terminal peritonitis. The maternal illness is not mentioned in the

available case notes, and the only joints described as abnormal are the wrists. The death certificate diagnosis was Still's disease.

Case 4.—A 31-year-old woman with two previous normal pregnancies and a 14-week miscarriage developed mumps at seven weeks' gestation, the infection being described as severe. A 3,770-g girl was born at 41 weeks' gestation after an otherwise normal pregnancy. Nothing more is known of the child until age 13, when she presented with a tender swelling of the rib cage. This was removed, but numerous pleural metastases were noted at operation. Histological examination showed the lesion to be Ewing's tumour. There was an initial response to radiotherapy but other metastases soon became evident and the child died eight months after diagnosis. The death certificate diagnosis was Ewing's sarcoma of rib.

Case 5.—Maternal rubella. The child was accidentally killed.

Case 6.—Maternal rubella at eight weeks. The child was born with subpulmonary stenosis and patent foramen ovale (later closed surgically). The patient died in cardiac failure aged 17 years. Death certificate diagnosis was congenital heart disease—subpulmonary stenosis.

Case 7.—Maternal rubella at 15 weeks; no other details of pregnancy available. The patient died at home aged 14 years. The death certificate diagnosis was status asthmaticus.

Discussion

The study set out to look for the possible association between virus infections in pregnancy and the subsequent development of leukaemia in the child. To test the significance of the findings in this light the numbers of deaths observed are compared with those to be expected on the basis of the average national experience of children followed from age 2 in 1954 to age 19 in 1971 in England and Wales. The number of deaths expected were calculated for leukaemia, for all cancers, and for all causes (see table). For all causes in all groups 9.09 deaths were expected;

Expected Numbers of Deaths in Children Followed from Age Two in 1954 to age 19 in 1971 Based on Statistics for England and Wales with Correction for Emigration (Estimated Loss 2.5%). Observed Numbers are Shown in Parentheses

	Chickenpox (270 Cases)	Mumps (433 Cases)	Rubella (303 Cases)	All (1,006 Cases)
Leukaemia/lymphoma	0.15 (2)	0.24 (-)	0.17 (-)	0.55 (2)
All malignant disease (including above)	0.36 (2)	0.57 (1)	0.40 (-)	1.33 (3)
All other causes	2.08 (-)	3.34 (1)	2.34 (3)	7.77 (4)
All causes	2.44 (2)	3.91 (2)	2.74 (3)	9.09 (7)

seven were found, a result which does not differ significantly from the expected. The causes of death among the rubella index cases were not remarkable, but those from the other two groups were. Both deaths of chickenpox index cases were from leukaemia, a statistically significant excess ($P < 0.01$). The causes of death in the mumps index cases were noteworthy because of their rarity. In England and Wales there was only one childhood death from Still's disease in each of the years 1968 to 1971 (data relating to the time when case 3 died are not available), and only 17 cases of Ewing's sarcoma were diagnosed in 1968.

Since we set out to test whether virus infections in pregnancy are related to leukaemia in the children, we conclude that in the case of chickenpox infection the hypothesis is sustained. In the case of the other infections it is not, but it should be noted that our sample sizes do not exclude a risk of one case per 200 to 250 virus infections—that found for influenza by Fedrick and Alberman (1972).

By accepting the positive finding, one difficulty is involved. If the two leukaemia deaths were due to maternal chickenpox they should be deaths over and above the "expected" number of deaths, yet no other deaths were found in this group. The death from congenital heart disease may presumably be attri-

buted to rubella, and according to whether the cases of Ewing's tumour and Still's disease are believed to have been due to mumps there are only two, three, or four deaths unrelated to the infections. A possible explanation for some of the deficit is that the pregnancies studied included fewer than "expected" from social classes IV and V (as defined by the Registrar General) where child mortality is highest. Such a bias, however, would not influence the argument on leukaemia because childhood leukaemia does not vary with social class. Despite the difficulty in interpreting the causes of these few deaths we incline to accept the finding which is positive and in keeping with the hypothesis that chickenpox in pregnancy is related to leukaemia in the child. So far as we know this association has not been reported before, although Stewart *et al.* (1958) noted two cases of leukaemia after herpes zoster in pregnancy. (They also noted one leukaemia case after mumps.) The conclusion is strengthened by the finding (Fedrick and Alberman, 1972) that cases of influenza in pregnancy were followed by a greatly increased number of diagnoses of leukaemia in the children, and also by previous reports of the effects of other virus infections. Stewart *et al.* (1958) noted leukaemia after maternal infectious hepatitis and lymphoblastoma after rubella.

Our findings and those mentioned above (supported by what is known from animal experiments) show that a proportion of childhood leukaemia cases are associated with virus infections; the disease may even be a nonspecific reaction to virus infection in pregnancy. It remains to be shown whether different infections carry different risks, and whether certain groups affected by the same virus are at special risk. In this respect we do not know whether there is any significance in the recorded statement that the mother in case 1 was suffering from chickenpox for the second time. Furthermore, since the cases reported by Fedrick and Alberman (1972) may have occurred as early as 12 weeks of gestation and as late as 36 weeks, no critical period

in gestation is yet evident, and it would be reasonable to question whether virus infections in early infancy have similar properties.

While we do not know whether either of the deaths in the mumps index cases was more than coincidentally related to the preceding infection it is reasonable to suspect that virus infections in pregnancy may have other undiscovered effects which may well include Still's disease or Ewing's tumour. That infant mortality from respiratory disease increases after influenza epidemics (Griffith *et al.*, 1972)—an observation that has yet to be elucidated—shows that such effects can have remained undiscovered until the present.

Further investigation of the type described in this study will define which virus infections from what stages of pregnancy can lead to leukaemia and shed light on its pathogenesis with real hope for prevention or cure. It will also show what other complications can follow these infections. We have, therefore, started collecting records of further cases of chickenpox, mumps, rubella, influenza, and other virus infections in pregnancy and in infancy, to show which virus infections lead to leukaemia, and in these cases to estimate the risk and define the danger period.

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Incidence of Neoplasms in Children Born after Influenza Epidemics

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Summary

Following a recent report that neoplasia of the lymphatic and haematopoietic tissues is commoner than average in children whose mothers have had influenza in pregnancy, the incidence of neoplasms in 1954-68 in children of the Manchester Hospital Region was examined in relation to date of birth. There were no significant differences between cohorts born in different quinquennia. Incidence among children born after six influenza epidemics in 1951-68 was no higher than among other children born in these years. It is concluded that if there is an association between maternal influenza and childhood neoplasia it is probably due to factors such as immunological deficiencies which may predispose independently to both conditions.

Introduction

It has been suggested that children whose mothers have had influenza in pregnancy may be more likely than average to develop neoplasms of lymphatic or haematopoietic tissue (Fedrick and Alberman, 1972). The suggestion was prompted by two observations. Firstly, in a longitudinal study the incidence of these neoplasms in children whose mothers had given a history of influenza when questioned soon after delivery was found to be higher than in other children. Secondly, the statistics published routinely by the Registrar General for England and Wales suggested that the mortality from these neoplasms at ages under 5 years had been higher than average in children born in years that began during winters when influenza epidemics occurred.

The value of the statistics on year of birth was, however, rather limited, firstly, by being based only on death certificates and not allowing for survivors or for errors in certification, and, secondly, by the fact that the Registrar General does not analyse deaths by year of birth, but only by year of death and age. The numbers born in different years were estimated by halving the number of deaths recorded for each age group and calendar year and allocating half to the first and half to the second of the two years in which the relevant children could have been born.

To remedy these deficiencies we have explored the possible relation of influenza epidemics to the births of children recorded

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