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Influenza Infections During Pregnancy: Association with Congenital Malformations and with Subsequent Neoplasms in Children, and Potential Hazards of Live Virus Vaccines

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INTRODUCTION

There have been a number of contradictory reports concerning the association of influenza virus infections during pregnancy with congenital malformations and with subsequent neoplasms of lymphatic and hematopoietic tissues in childhood (International Classification of Diseases 200-209). Clinical trials of live influenza vaccines are underway, or being actively considered, in several countries, and the possibility of their widespread future use makes it increasingly important to determine the dangers they might represent during pregnancy, either by direct vaccination or by transmission from a vaccinated individual. The purpose of this communication is to compare and summarize the available information in an attempt to delineate the possible consequences of live influenza vaccines.

ASSOCIATION OF INFLUENZA INFECTIONS DURING PREGNANCY AND CONGENITAL MALFORMATIONS

Problems in Interpretation

The contradictory evidence for and against the association of influenza infections during pregnancy with congenital malformations may be explained in part by the methods employed in the collection and classification of data. In general, the various investigations fall into one of two categories, prospective or retrospective studies. Prospective studies were often too small to provide adequate evidence of a causal relationship, whereas retrospective studies depended on the recognition of an abnormality at birth and its subsequent association with a disease which might have occurred during early pregnancy, or, in the larger epidemiological surveys, with the incidence of congenital abnormalities following an influenza epidemic compared to the incidence in nonepidemic periods. The information was usually obtained from one of three sources: from self-diagnosis and self-reporting by means of questionnaires or interviews; from clinical diagnosis; or from hospital or national records. Each of these methods can be inaccurate and misleading without more precise diagnostic techniques, such as serological evidence of infection, but only a small minority of studies have employed serological techniques. Mild or subclinical infections would, therefore, have been missed. This was well documented in a prospective investigation

of 671 patients by Hardy et al. (20) during the 1957–1958 influenza epidemic in Baltimore. Of 373 patients who had a history of an "influenza-like" illness, all but 24 had serological evidence of infection, but 222 of 298 patients who had no history of such illness were also found to have serological evidence of infection. A similarly high proportion of mild or subclinical cazses was reported by Walker and McKee (43).

Self-diagnosis by questionnaire or interview must be considered of doubtful value in the assessment of influenza infections. Any heavy cold is normally construed by many as being "influenza." In our experience during an epidemic of influenza in Western Australia in 1973, over 75% of volunteers taking part in a clinical trail of a live influenza vaccine who claimed to have experienced "influenza-like" symptoms had no serological evidence of infection. Another bias could also arise in retrospective studies conducted by questionnaire in that mothers bearing children with abnormalities might be more likely to remember illness during early pregnancy than those with normal children. Even in the face of an epidemic, clinical diagnosis by a physician must be considered unreliable, as many other viral and bacterial infections can mimic the broad spectrum of influenza symptoms. Once again, mild and subclinical cases would remain undiagnosed.

Thus, two major problems are evident in assessing those reports which have suggested an association between influenza and congenital malformations: the lack of definitive evidence of influenza infections, and the bias towards severe cases of "influenza-like" illness to the exclusion of mild and subclinical infections.

Evidence for and Against an Association

The reports describing a putative association between influenza during pregnancy and malformations and for which case figures are available are shown in Table 1; those reports which were unable to substantiate such an association are shown in Table 2. The only period during which a fetus might be susceptible to major malformations, such as central nervous system (CNS) abnormalities, is during the first trimester of pregnancy. The published results, therefore, have been tabulated by the degree of risk involved: influenza during the first trimester, influenza at other times during pregnancy, or control cases where there was no record of influenza. The evidence for or against specific abnormalities is shown in Table 3.

CNS malformations. An indication that there might be an association between influenza and congenital malformations was first observed by Coffey and Jessop (6) in a retrospective investigation in Dublin during 1953. A history of "influenza-like" symptoms was obtained five times as often from mothers of abnormal babies as from controls. This finding was extended in a second prospective investigation during the 1957 Asian influenza epidemic (7, 8). Women attending ante-natal clinics in three Dublin hospitals were asked whether they had experienced an "influenza-like" illness and, if so, the date of the illness. Appropriate control cases were included who had not had influenza and who were at the same stage of pregnancy. A significant increase was observed in the incidence of CNS malformations (anencephaly and spina bifida) in the influenza group, and the increase was greatest if the illness took place in the first trimester (Tables 1 and 3). The numbers concerned, however, were relatively small, and the incidence of CNS malformations in the control group was much higher than the normal incidence elsewhere in both epidemic and nonepidemic periods. A significant increase in CNS malformations was also reported in Finland among women who were in their first trimester of pregnancy at the time of the 1957 Asian influenza epidemic (17, 40), but the incidence was well below that described in Dublin, and the authors suggested that a more plausible explanation might rest with some other agent contingent on the disease (Tables 1 and 3). The overall incidence of congenital abnormalities was not found to increase significantly.

If there is an association between influenza and CNS malformations, particularly at the high incidence rate reported in Dublin, it should be evident in large-scale retrospective epidemiological surveys. Leck and his colleagues (27–29) determined the incidence of different types of congenital malformation in Birmingham and in several areas of the United States by comparing the incidence 6 to 9 months after an influenza epidemic, when influenza-induced abnormalities would be expected, with a similar period in nonepidemic years. No increase in the incidence of CNS malformations was noted after any of the influenza epidemics between 1957 and 1968 (Table 3). Leck (27) also analyzed the stillbirth statistics between 1951 and 1960 published by the Registrar-General of Scotland, but again was unable to provide evidence of an association between influenza epidemics and CNS malformations, confirming a previous analysis by Record (36). This was in contrast to an interpretation of the same data by Doll, Hill, and Sakula (10), who noted a secular bias and an unusually high incidence of CNS malformations in 1958 following the 1957 influenza epidemic. The period of increased

TABLE 1. *Major publications for which sufficient figures are available proposing a positive association between congenital abnormalities and influenza virus infections during pregnancy*

Method of assessment of influenza cases	Author	Date of epidemic	Influenza during 1st trimester			Influenza before or after 1st trimester			No influenza recorded			Type of malformation possibly associated with influenza infection
			Observed no. of malformed	No. at risk in population studied	Per cent malformed	Observed no. of malformed	No. at risk in population studied	Per cent malformed	Observed no. of malformed	No. at risk in population studied	Per cent malformed	
Serological	Hardy et al. (20)	1957/58	8	75	10.7	15	458	3.3	1	73	1.3	General
Inquiry before birth (prospective)	Coffey and Jessop (7)	1957/58	8	108	7.4	16	554	2.9	10	663	1.5	Malformation of the CNS
	Pleydell (35)	1957	1	10	10.0	2	31	6.5	14	1,030	1.4	Possible malformation of the CNS
Inquiry before and after birth	Hakosalo and Saxen (17)	1957/58	57[a]	1,603	3.55	70	2,343	3.0	73	2,201	3.31	CNS and circulatory malformations
			28[b]	1,603	1.75	18	2,343	0.77	23	2,201	1.04	
	Leck (27)	1957/58, 1959, 1960/61	225[a]	22,698	0.99	—	—	—	714	79,344	0.90	Cleft lip and reductive deformities
			49[c]	22,698	0.22	—	—	—	116	79,344	0.15	
Inquiry after birth (retrospective)	Leck (28)	1966, 1967/68	2,942[a]	572,535	0.51	—	—	—		8,763	0.50	Cleft lip and reductive deformities
			351[c]	572,535	0.06	—	—	—	930	1,756,107	0.05	
			Influenza recorded, trimester not stated									
			No. of malformed	No. at risk	Per cent malformed							
	Coffey and Jessop (6)	1953	40	519[d]	7.7				177	12,833[d]	1.4	CNS malformations

[a] All malformations.
[b] CNS and circulatory malformations only.
[c] Cleft lip and reductive deformities only.
[d] Estimated by Leck (27).

TABLE 2. *Major publications for which sufficient figures are available exhibiting a negative association between congenital abnormalities and influenza virus infections during pregnancy*

Method of assessment of influenza cases	Author	Date of epidemic	Influenza during 1st trimester			Influenza before or after 1st trimester			No influenza recorded		
			Observed no. of malformed	No. at risk in population studied	Per cent malformed	Observed no. of malformed	No. at risk in population studied	Per cent malformed	Observed no. of malformed	No. at risk in population studied	Per cent malformed
Serological	Wilson and Stein (46)	1957/58	4	299	1.3	—	—	—	3	188	1.6
Inquiry before birth (prospective)	Campbell (5)	1950/51	3	122	2.5	1	41	2.4	12	825	1.5
	Doll, Hill, and Sakula (10)	1957/58	2	63	3.2	2	66	3.0	0	48	0
			Influenza recorded but trimester not stated								
			Observed no. of malformed	No. at risk in population studied	Per cent malformed						
Inquiry after birth with serology	Walker and McKee (43)	1957	6	214	2.8				7	184	3.8
Not stated	Abramowitz (1)	1957	3	315	1.0				5	414	1.2

TABLE 3. *Evidence for and against specific abnormalities being associated with influenza virus infections during pregnancy (1st trimester)*

Type of abnormality	For or against an association	Author	Influenza during 1st trimester			No influenza recorded		
			Observed no. of malformed	No. at risk in population studied	Per cent malformed	Observed no. of malformed	No. at risk in population studied	Per cent malformed
CNS malformations	For	Coffey and Jessop (6)	<8[a]	108	<7.4[a]	7	663	1.06
		Hakosalo and Saxen (17)	13	1,603	0.81	7	2,201	0.32
		Pleydell (35)	1	10	10.0	3	1,040	0.29
	Against	Leck (27)	110	22,698	0.48	426	79,344	0.54
		Leck (28)	1,798	572,535	0.31	5,556	1,756,107	0.32
		Leck et al. (29)	237	200,000	0.12	2,247	1,884,100	0.12
Circulatory malformations	For	Hakosalo and Saxen (17)	15	1,603	0.94	16	2,201	0.73
		Hardy et al. (20)	3	75	4.0	—[b]	—[b]	—[b]
Cleft lip	For	Leck (27)	236	572,535	0.041	631	1,756,107	0.036
		Leck (28)	18	14,747	0.12	10	14,612	0.068
		Leck et al. (29)	62	200,000	0.031	464	1,884,100	0.025
Reductive deformities	For	Leck (27)	14	22,698	0.062	35	79,344	0.046
		Leck et al. (29)	72	200,000	0.036	516	1,884,100	0.027
		Leck (28)	115	572,535	0.020	299	1,756,107	0.017

[a] Type of malformation during first trimester not stated, but 6 of 24 recorded malformations were not CNS malformations.

[b] No details provided.

incidence, however, did not correlate with the epidemic if malformations were the result of infection during the first trimester. Similarly, there was no correlation between increased incidences of CNS malformations and influenza epidemics in South Wales from 1956 to 1962 (26), or between the monthly stillbirth figures (88% of which were CNS malformations) and death rates from influenza in England and Wales from 1961 to 1970 (39). In the latter report, Rogers also calculated the increase in still births that might be expected in England and Wales following the 1969–1970 epidemic if the same increase in incidence of CNS malformations experienced in Finland in 1958 by Hakosalo and Saxen (17) had occurred, but no such increase was observed.

In other reports which have described specific congenital abnormalities in women with a history of influenza during the first trimester (10, 12, 20, 43, 46), the incidence of CNS malformations was no greater than in control groups with no record of influenza. Pleydell (35), however, suggested that the incidence of CNS malformations in Northamptonshire could best be explained by an infectious disease, but the only evidence for the implication of influenza was one case of hydrocephaly in 10 first-trimester infections.

Thus, the evidence for an association between influenza infections during the first trimester and CNS malformations is confined to reports by Coffey and Jessop (6, 7) and Saxen and his colleagues (17, 40). The incidence in the control group in Dublin, however, was higher than normal. It has been known for some time that neural tube malformations involve both hereditary predisposition and environmental factors, and that a strong seasonal variation in incidence can be found in certain areas. It is possible, therefore, that influenza may have played a secondary role in both Dublin and Finland by acting as an environmental trigger under specific and unusual conditions.

Circulatory malformations. Hakosalo and Saxen (17) found slight suggestive evidence of an increase in circulatory malformations following influenza infections during the first trimester (Table 3). No other investigation has provided data in support of their observation, although three cardiac malformations were recorded by Hardy et al. (20) among 75 cases with

serological evidence of influenza infections during the first trimester.

Cleft lip and reduction deformities. A significant increase (more than 10%) in the incidence of cleft lip and reduction deformities, particularly of the fingers, was observed in retrospective epidemiological investigations on congenital malformations in Birmingham and the United States following various influenza A_2 and B epidemics between 1957 and 1968 (Tables 1 and 3; 27–29). The incidence of cleft lip, however, did not increase after the initial Asian epidemic in 1957, and the increase in the incidence of reduction deformities occurred only after influenza A epidemics. Leck (28) suggested that the association of cleft lip with outbreaks of familiar influenza strains, rather than new strains, might be caused by some event that happens in the presence of residual levels of immunity.

The incidence of malformations was calculated on the assumption that the first trimester of intra-uterine life constituted the high-risk category, and that any increased incidence, therefore, must occur 26 to 40 weeks after each epidemic. Thus, the association between influenza and congenital malformations could be ascertained by the difference between the incidence of each specific malformation 26 to 40 weeks after an epidemic and the incidence over the same months in nonepidemic years. If the period from 26 to 40 weeks is divided into four monthly phases, a causal relationship between influenza and cleft lip or reduction deformities should result in an increased incidence in the same phase, or perhaps two adjacent phases, following each of the epidemics, corresponding to children at the same stage of development. However, no such consistency was observed, and Leck (28) interpreted this as evidence against a causal relationship. Even if a causal relationship does exist, the risk of cleft lip should be regarded as minimal, being in the order of one excess abnormality in 24,000 births.

Other reports suggesting an association between influenza and congenital malformations. In a prospective inquiry in Watford between 1952 and 1955 into maternal health during early pregnancy and congenital defects (31), 127 of the women interviewed claimed to have experienced a febrile respiratory illness in the first 12 weeks of pregnancy. Eight serious malformations were recorded, which was slightly more than twice the incidence found in women with no history of febrile illness, but no information was supplied on the type of malformations other than the absence of anencephaly. The author concluded that the evidence suggested an association between congenital malformations and febrile illnesses, but that there was probably no direct causal relationship.

An eightfold increase in the general congenital malformation rate following Asian influenza infections during the first trimester was observed in a prospective investigation in Baltimore by Hardy et al. (20). Eight malformations were found among 75 women who had clinical and/or serological evidence of influenza (Table 1), the malformations being three cardiac, one twin holocardiac monster, three syndactylia, and one with a large area of hyperpigmentation. The interpretation of these results is difficult. The epidemic in Baltimore began in late September of 1957 and was widespread by the end of October. From mid-October until the end of January 1958, 671 patients were enrolled in the study. At each monthly visit to the prenatal clinic, they were asked to complete a questionnaire to determine whether they had experienced "influenza-like" symptoms, and a blood sample was drawn. Thus, the investigation began after the start of the epidemic, and patients were still being included when the epidemic had finished. Of the 373 patients who had a history of "influenza-like" illness, all but 24 had serological evidence of infection. However, 222 patients who had no such history of illness were also found to have serological evidence of infection, which left a small control group of 73 women with no evidence of infection. The influenza attack rate was 85%, a figure higher than has been reported in most areas. A diagnostically significant fourfold rise in antibody titer was obtained from only 61 individuals, but it should be remembered that the epidemic was caused by an antigenically novel virus, and no one in the age groups involved would have had prior experience of it. Nevertheless, an absence of a fourfold antibody rise could lead to inaccuracies in determining the trimester of infection, particularly in those women who had no clinical history of "influenza-like" illness. If the results of the investigation are analyzed without differentiating the trimester of infection, and including the patients with no clinical evidence of disease in the control group, no association is apparent between influenza and congenital malformations, nor is there any difference in stillbirths and neonatal death rates between those with a history of "influenza-like" illness and the incidence in previous years. The difficulties in interpretation, therefore, rest largely on the high attack rate and low control numbers, the enforced lack of serological precision, and the unusually broad spectrum of malformations.

Reports unable to substantiate an association between influenza and congenital malformations. A number of investigations have been unable to provide evidence for a positive link between influenza and congenital malformations. Although some of these investigations examined the incidence of specific types of malformations, such as those affecting the CNS which were mentioned previously, the majority were concerned with the overall incidence of general malformations, and in particular the incidence that followed the 1957-1958 Asian influenza epidemic.

The first study was made by Campbell (5) during an outbreak of A_1 influenza in Belfast in 1950-1951. The investigation was prospective and only included women who were in their first few months of pregnancy at the time of the epidemic. "Influenza-like" infections were ascertained by interview and, to be acceptable, had to be severe enough to cause the patient to be confined to bed. A total of 989 births were recorded, and, although the incidence of malformations was slightly higher in the group that experienced "influenza-like" symptoms during the first trimester (Table 2), it was not regarded as significant. The three malformations observed in this group were one hydrocephalic, one clubfoot, and one absence of kidney.

The effect of the Asian influenza epidemic on the outcome of pregnancy in Cape Town in 1957 was assessed by Abramowitz (1). To be classified as having had influenza, women in the first 20 weeks of pregnancy had to have been confined to bed for at least 1 day during the epidemic period. Three minor abnormalities were reported in 315 "influenza" cases, and four minor and one major abnormality occurred among the 414 control cases (Table 2), but the types of abnormality were not stated.

An increase in the incidence of congenital malformations could not be demonstrated retrospectively among children born 7 to 8 months after the 1957 epidemic in either Pennsylvania (24) or New York City (23, 44), nor in five subsequent epidemics between then and 1961 in New York City (44). In the latter report, serological techniques were employed to study 1,264 women between March 1960 and April 1961, a period which would have shown a possible effect caused by the 1960 epidemic, but no increase in the incidence of malformations was found in any of the three groups examined (a fourfold increase in antibody titer; no increase and with a low initial titer; no increase but with a high initial titer). The results were not analyzed to determine incidence at different stages of pregnancy, and no details were provided on the types of malformation observed.

Walker and McKee (43) investigated the outcome of pregnancy retrospectively in Iowa after the 1957 epidemic. Women were interviewed shortly after giving birth to determine those who had experienced "influenza-like" symptoms, and a blood sample was taken from those that had. Blood samples were also drawn from all mothers of infants with congenital abnormalities and from 101 other patients whether or not they had experienced "influenza-like" symptoms. By these means, 158 of 297 mothers admitted to having experienced "influenza-like" symptoms, and 154 of the 158 were found to have antibody titers to one or more of several isolates of the Asian virus. Thirty-one of the mothers with a negative history of influenza also had blood drawn, and, with the other 101 patients included, it was found that all but one had serological evidence of infection. The influenza attack rate, therefore, was extremely high. In the entire series of 398 mothers, 13 malformations were observed, but only 1 had experienced "influenza-like" symptoms in the first trimester (multiple congenital anomalies of the left hand and right foot and leg). In 5 of the other 12 instances of malformation, the influenza-like symptoms occurred after the first trimester (1 clubfoot, 1 cleft lip, 1 spina bifida, 1 cleft palate, and 1 varicosities on the chest wall), and in the remaining 7 instances all mothers had serological evidence of infection but were asymptomatic.

Interpretation of these results was hampered by the retrospective nature of the investigation since it was impossible to date the time of infection of asymptomatic patients. However, grouping the 214 patients who reported "influenza-like" symptoms together as having had influenza but with trimester unknown and grouping the remaining 184 patients as not having experienced influenza revealed no increase in the incidence of malformations (Table 2). The authors inferred that even if asymptomatic patients were included in the influenza group the incidence was not significantly greater than might be expected in nonepidemic periods.

The addition of serological evidence, as well as a history of "influenza-like" symptoms, was employed in an investigation in Los Angeles by Wilson and her colleagues following the 1957 epidemic (45, 46). Only women who conceived during the 3-month epidemic period were included in the study. They were interviewed to determine whether they had experienced "in-

fluenza-like" symptoms, and blood samples were drawn during their second trimester. The pregnancy outcome was monitored for 487 mothers of whom 299 had serological evidence of infection during their first trimester. Four anomalies were observed among the infants born to women with serological evidence of infection (one with cleft lip and palate, one with bladder neck obstruction, and two with anencephaly), and three anomalies occurred in the control group with negative titers (one with phocomelia, one with renal hypoplasia, and one with cleft palate). There was no increase in incidence in the influenza group (Table 2), but three of the abnormalities were of the same type as those associated with influenza in other investigations (anencephaly and cleft lip). The number of patients in the influenza group might be slightly exaggerated for two reasons: a few who were included during the third month of the epidemic could have had prior exposure to influenza; and, since blood specimens were drawn throughout the second trimester, some patients may have had exposure after the first trimester.

No association was detected between influenza and congenital malformations in a study in north-west London after the 1957 epidemic (10). Women were interviewed to determine whether they had suffered an attack of "influenza-like" illness, and where possible a diagnostic confirmation was obtained from their local practitioner. A total of 128 women were regarded as having suffered an attack of "influenza," and for 63 of them it occurred during their first trimester. Two congenital malformations were observed in this group: one with hypospadias, and one with a congenital heart lesion and a possible cerebral haemorrhage (Table 2). A further 66 women suffered "influenza" either shortly before pregnancy or after the first trimester, and again two abnormalities were reported: one with a harelip and extensive naevus on the left side of the face, and one with an extra digit to the right fifth finger. The influenza attack rate was believed to be 21% (128 women with "influenza-like" symptoms among 606 women).

Evidence from Animal Models

Animal models have proved to be of limited value in assessing the teratogenicity of influenza in humans in the two systems which have been investigated: chick embryos and mice.

Inoculation of early chick embryos with two A_0 strains of influenza virus, NWS and PR8, produced a number of malformations including microencephaly, axial flexion, retardation of the lens, and myeloschisis (19, 22, 38). However, the relevance of these results to the human situation cannot be readily assessed since the embryos were inoculated directly through the vitelline membrane and the production of malformations was dependent on viral concentration. It is not known whether influenza is able to cross the placental barrier in women during the first trimester (see below) or, if it can, what concentration of virus is required to cause fetal damage. Similar malformations in the chick embryo were observed with vaccinia virus (22), but, although vaccinia can cross the human placenta during the first trimester and cause fetal death in some cases, there have been no reports of any association with congenital malformations (15).

Congenital malformations were produced in Swiss albino mice inoculated intranasally with sublethal doses of the PR8 strain of influenza either immediately before or 4 days after mating (2), but no details were provided of the types of malformation. In a further study from the same laboratory (41), malformations were not observed in mice inoculated with high, lethal doses of virus by the intranasal, intraperitoneal, or intravenous routes during the second or third trimester. Evidence of transplacental tranmission was found, but only during the third trimester.

Discussion

A number of difficulties exist in assessing the reports described above. Some of these difficulties have been mentioned previously as being inherent in the methods employed in the collection of data, but the others become more evident as the data provided in the various reports are compared.

The most immediate and obvious question which arises concerns the reasons why certain malformations should be observed in some investigations and not in others. An increase in the incidence of anencephaly and other CNS malformations was observed in Dublin (6–8) and Finland (17, 40), but not elsewhere; a possible increase in the incidence of circulatory malformations was observed in Finland (17) and, as part of a general increase in malformations, in Baltimore (20); and an increase in incidence of cleft lip and reduction deformities was observed in Birmingham (27), the United States (29), and England and Wales (28). All of these malformations are found in the general population in nonepidemic periods and, unlike the malformations caused by rubella and other

known teratogenic agents, cannot be regarded as constituting a specific syndrome. Anencephaly has been shown to have a highly secular incidence, and, although it might be consistent with an infective agent as the cause (36), it has not been possible to implicate influenza (26, 27, 36). Other factors are known to be important in anencephaly such as genetic predisposition, the age of the mother, and a higher incidence in female to male births. None of these factors was analyzed in Finland or Dublin in relation to the cases of malformation. It is also interesting to note that in both reports by Coffey and Jessop (6, 7) the births studied occurred in three hospitals, and the incidence of CNS malformations in one of the hospitals, the Rotunda, was no greater in the group which had experienced "influenza-like" symptoms than in the control group. This would suggest that influenza was not the cause of the increased incidence observed in the other two hospitals, and supports the contention of Rogers (39) that at certain times and places there is a high spontaneous incidence of CNS malformations (the incidence of CNS malformations in the control group in Dublin was considerably higher than normal).

An increase in circulatory malformations was more suggestive than actual, but, because of the methods employed in the majority of the investigations, a possibility must exist that such malformations were under-recorded since many of them would not have been diagnosed until later in childhood.

With the exception of Hardy et al. (20), all the investigations implicating influenza infections with an increased incidence of malformations have depended either on a clinical diagnosis by questionnaire or interview, or on differing incidence rates between epidemic and nonepidemic periods. As stated previously, the former would not have included mild and subclinical infections. Influenza attack rates, therefore, assume great importance. Those based on clinical diagnosis and morbidity must be considered doubtful since they, too, would not have included mild and subclinical cases. From serological evidence, the attack rates among the patients studied in Baltimore (20) and Iowa (43) were over 80%, and in Los Angeles, 60% (46). If similar rates occurred in Dublin and Finland, a considerable dilution in the incidence rates of the clinical influenza cases would be expected.

Other suggestions have been made to account for the increased incidence of malformations in Dublin and Finland, including drugs such as salicylate-containing preparations (42) and hyperthermia (11). There is slight suggestive evidence that salicylates might be teratogenic (37), but hyperthermia has been shown by Edwards (11) to cause many malformations in guinea pigs and rats, including anencephaly. Neither of these suggestions would require transplacental transmission (see below), and only severe cases of influenza would need to be implicated.

In the absence of precise etiological diagnosis with the inclusion of mild and subclinical infections, and because of the unusual geographical incidences of types of malformation, it is our opinion that no direct association between influenza infections during pregnancy and congenital malformations can be substantiated, other than cleft lip and reduction deformities. Nevertheless, an indirect association might exist in collaboration with environmental factors or a genetic predisposition.

ABORTION AND STILLBIRTHS WITHOUT MALFORMATION

There is little evidence to suggest that abortions, stillbirths without malformation, or prematurity are associated with influenza infections during pregnancy, except for one investigation by Harris (21) following the 1918–1919 pandemic, in which he reported a profound effect in the pregnancy outcome of 1,350 women. Termination by abortion, stillbirth, or prematurity occurred in 26% of the cases that were not complicated by pneumonia and rose to 52% in the cases that were complicated. Hardy et al. (20) observed a slight increase in the number of abortions and stillbirths following influenza infections in the first trimester, but the number of patients involved was too small to be significant. No increase was seen following infection later in pregnancy. Wilson and Stein (46) also observed a slight increase in the number of stillbirths, 7 from 299 mothers with serological evidence of influenza compared to 3 (including one twin) from 188 control mothers. Two abortions (one at the fourth month of pregnancy and one at the sixth month) were recorded by Pleydell (35) from 12 mothers with "influenza-like" symptoms during pregnancy. McDonald (31) found a significantly increased incidence of abortion among mothers who had a febrile illness during the first 12 weeks of pregnancy and a slight increase in the incidence of stillbirths.

No increase in the incidence of abortion, stillbirths, or prematurity was observed in other investigations (1, 5, 23, 44).

MATERNAL RISK DURING PREGNANCY

Harris (21) reported a maternal mortality rate of 27% during the 1918 pandemic which increased to 50% when complicated by pneumo-

nia. Such an abnormally high mortality rate has not been observed since (probably with the advent of antibiotic therapy), although several authors reported higher mortality rates in pregnant women than in nonpregnant women during the 1957 epidemic. Greenberg et al. (16) found that approximately half of all influenza deaths in women of childbearing age in New York City were women who were pregnant. This was confirmed in reports by Freeman and Barno (14) in Minnesota and by Widelock, Csizmas, and Klein (44) in New York City. In the latter report, there was a ninefold increase in maternal deaths in the 20- to 29-year age group, but only during the 1957 epidemic. No increase in maternal deaths was observed during subsequent epidemics up to 1961.

Influenza mortality associated with pregnancy may be caused by a primary edematous pneumonia, in contrast to deaths in men and nonpregnant women, where secondary bacterial infections are more important (14). It has been suggested that this may be due to a decrease in nonspecific protective factors in pregnant women, but which may be offset by residual immunity from a prior exposure. No prior exposure was possible before the 1957 epidemic because of the novel antigenicity of the Asian virus, and the mortality rates, therefore, were increased, but residual immunity was probably present in the majority of the population in subsequent epidemic periods and offered protection during pregnancy.

ASSOCIATION OF INFLUENZA INFECTIONS DURING PREGNANCY WITH CHILDHOOD CANCER

There have been three reports proposing an association between influenza infections during pregnancy and malignant disease in children, and one report in which an association could not be detected. Once again, the retrospective nature of the investigations presented problems in assessing and comparing the evidence, including the uncertain clinical diagnosis of influenza, the lack of information on subclinical and mild infections, and the inherent uncertainty of the influenza attack rate with its correlation to severe infections only.

The first investigation to suggest that such an association might exist was reported by Fedrick and Alberman (13) from a longitudinal study of 16,750 children born in a single week during March 1958 in Britain. The mothers of 1,959 children recorded "influenza-like" symptoms during pregnancy, which must have occurred during the second and third trimesters since the Asian influenza epidemic was prevalent at the end of 1957 and the beginning of 1958. Eight cases of malignant disease were observed among this group (an incidence rate of 4.1 cases per 1,000 births) compared to 12 cases among the 14,791 children whose mothers did not record an influenza infection (a rate of 0.8 per 1,000). When the types of malignancy were examined, 7 of the 8 cases with a history of maternal influenza were found to be neoplasms of the lymphatic and hematopoietic tissue (International Classification of Diseases 200–209), an incidence of 3.6 per 1,000, whereas only 6 of the malignancies reported in the children without such a history fell into these categories, an incidence of 0.4 per 1,000. Thus, a fivefold increase in the incidence of all malignancies appeared to follow a history of maternal influenza during pregnancy, and a ninefold increase occurred in neoplasms of lymphatic and hematopoietic tissue. An examination of the ages at which the first symptoms were observed in the International Classification of Diseases 200–209 cases, revealed a mean of 7.4 years when there was a history of influenza and a mean of 4.3 years in the control group. This was not believed to be significant.

Fedrick and Alberman (13) also analyzed the data from the reports of the Registrar-General for England and Wales to estimate the number of children born in each year from 1955 to 1964 who subsequently died of cancer before 5 years of age. An overall secular decrease in death was observed which was believed to be due to a prolongation of life resulting from improvement in treatment. However, by allowing for this trend, they obtained a correlation between children dying from neoplasms of lymphatic and hematopoietic tissue and an influenza epidemic in the year preceding their birth which was statistically highly significant. A less significant correlation was observed for children dying from all types of cancer.

The validity of these latter results is open to criticism for three reasons. Although the ages of children dying from cancer was provided by the yearly statistics published by the Registrar-General, the dates of birth were not. The possible birth date for each child, therefore, covered a 2-year period, and, to compute their yearly cancer rates, Fedrick and Alberman had to allocate half of each age group to each of the two years. Secondly, to determine the prevalence of influenza, the national yearly figures for certified incapacity among employed women due to influenza were used rather than epidemic attack rates. Finally, although the mean age for the onset of symptoms in the maternal influenza group after the 1957–1958 epidemic was 7.4 years, only deaths in children aged 5 years or under were included in the study.

An epidemiological survey in Finland (18) provided supporting evidence for an association between maternal influenza and childhood leukemia (International Classification of Diseases 204). Dates of influenza epidemics from 1952 to 1962 were ascertained from virus isolation records, and the morbidity of each epidemic was determined from absenteeism in Helsinki. Information on leukemia in children under the age of 10 years, including their dates of birth, was obtained from the Finnish Cancer Registry. The incidence of leukemia was then determined in children who were born during the 5 months following each influenza epidemic, whose mothers were therefore at risk to infection during pregnancy, and was compared to the incidence in children who were born 9 months after an epidemic and before the next outbreak. No differences were found in the incidence of leukemia between the 180,862 children born in the 5 months following epidemic periods and the 226,308 children born in control periods, the incidence of leukemia in each group being 0.44 per 1,000 births. However, when cases of leukemia in children born during the 5 months following the 1957 Asian epidemic were extracted from the records and compared to those in children born in control periods, a significant increase in the incidence of leukemia was apparent: 24 cases were recorded from 35,248 births, giving an incidence of 0.68 per 1,000 births.

Thus, in Finland, there was an apparent association between maternal influenza during the 1957 Asian epidemic and childhood leukemia but, contrary to Fedrick and Alberman (13), no such association was found with other influenza epidemics. The increase in incidence (55%) was considerably less than that reported by Fedrick and Alberman.

The results of an investigation by Bithell, Draper, and Gorbach (4), using retrospective data from the Oxford Survey of Childhood Cancers, also indicated an association between maternal influenza infections and malignant diseases in childhood, but the relative incidences of the different types of cancer were very different from the reports of Fedrick and Alberman and of Hakulinen and his colleagues. A 50% increase was found in the incidence of malignancies in general rather than a specific increase in the incidence of neoplasms of lymphatic and hematopoietic tissue, and, moreover, the ratio of International Classification of Diseases 200–209 cases to those of other malignancies was the same as the ratio observed in the control group studied by Fedrick and Alberman. When the cases were analyzed by trimester of infection, there was a slightly higher occurrence in the third trimester, but this was probably insignificant, and no correlation was observed between the time of infection and the types of malignancy. An association between maternal influenza and malignancy was found for all influenza epidemics studied, but the relative risk was marginally greater in the 1957 Asian epidemic.

The major problem in assessing these results is the very low number of cases recording influenza infections during pregnancy. The results were based on 9,074 cases of malignancy and an equal number of healthy controls matched for birth date, sex, and district of residence, but only 96 mothers of children with malignancies and 64 control mothers recalled having contracted influenza. It was suggested that this under-reporting was due to a delay, usually of several years, between pregnancy and the time that the mother was interviewed. Nevertheless, it is probable that many more mothers did, in fact, contract influenza, and one is forced to query the validity of both the positive correlation between malignancy and maternal influenza, and the increased incidence of all types of malignancy.

Leck and Steward (30) analyzed the incidence of childhood malignancies in residents of the Manchester Hospital Region below the age of 15 years in relation to six major influenza epidemics between 1950 and 1966. Only 1,158 children born in 1951–1968 could be included, and of these 435 had neoplasms of lymphatic and hematopoietic tissue and 723 had other types of neoplasm. No increase was found in the incidence of any or all malignancies in children born during or after each epidemic (calculated as standardized incidence ratios), or when compared with the incidence in children whose mothers were not at risk to infection.

A summary of the four reports described above is shown in Table 4 in terms of risk ratios, but it should be noted that the data from Leck and Steward are not strictly comparable because of the mathematical treatment used in their preparation. A number of significant differences are apparent among the reports, and, although some are obviously related to the methods employed in selecting and classifying data, they present an inconsistent pattern for any attempt to correlate cause and effect. Thus, Fedrick and Alberman (13) found a highly increased incidence of all neoplasms in Britain following the 1957 Asian epidemic, the majority of which were neoplasms of lymphatic and hematopoietic tissue, and they observed a strong correlation in other influenza epidemics

TABLE 4. *Summary of reports concerning an association between maternal influenza infection and subsequent childhood malignancies*

Author	Risk ratio	
	All cancers	Neoplasms of lymphatic and hemopoietic tissue (I.C.D. 200-209)
Fedrick and Alberman (13)	5.12	9.0
Hakulinen et al. (18)	—	1.54[b] 1.00[c]
Bithell et al. (4)	1.52	0.80
Leck and Steward (30)	1.00[a]	0.97[a]

[a] Standardized incidence ratios: not strictly comparable because of method of analysis. Figures were not available for a comparative re-analysis.

[b] International Classification of Diseases (I.C.D.) 204 cases only, 1957 epidemic.

[c] I.C.D. 204 cases, all epidemics.

between maternal infection and leukemia. An increase in the incidence of leukemias was also observed in Finland (18) in children born shortly after the Asian epidemic, but the increase was considerably less than that reported by Fedrick and Alberman, and no increase was detected in children born after other influenza epidemics. A similar degree of risk was reported by Bithell, Draper, and Gorbach (4), but it was a general increase in incidence of all malignancies and was not confined to specific types. The validity of these results was questioned on the grounds of an exceedingly low recall of maternal infections. Conversely, Leck and Steward (30) were unable to substantiate any association between maternal influenza and childhood malignancies.

Bithell and his colleagues suggested that the high incidence rates reported by Fedrick and Alberman were a chance finding since the week chosen for study in 1958 was associated with a much higher leukemia mortality than were the adjoining weeks. They also re-analyzed the national data used by Fedrick and Alberman, but on a monthly basis rather than an annual basis, and concluded that the relative risk was probably much lower than had been suggested.

It would appear, therefore, that an association between maternal influenza infections and subsequent childhood malignancies might exist, although the evidence is equivocal, but the inconsistent pattern of the various results would tend not to favor a direct causal relationship.

TRANSPLACENTAL TRANSMISSION

If an association exists between influenza infections during pregnancy and congenital malformations or childhood leukemia, the virus must either be able to cross the placenta or it must cause fetal damage by an indirect method such as through toxemia or metabolites from damaged cells. Viremia is a necessary prerequisite for transplacental transmission, and strong evidence exists for the occurrence of viremia in severe influenza infections, the virus having been isolated from extrapulmonary tissues (25, 27) and directly from blood (34). There is no published evidence to substantiate viremia in mild or subclinical infections, and in the latter it seems likely than an infection may be overcome at an early stage, possibly in the upper respiratory tract.

Transplacental transmission has been reported in a fatal case of influenza during the third trimester (47) and virus was isolated from fetal heart tissue and amniotic fluid. Monif, Sowards, and Eitzman (33), attempting to confirm transplacental transmission, studied the progeny in eight serologically documented cases of maternal influenza occurring in the second and third trimesters. However, they were unable to detect either an elevation of cord sera IgM levels or a persisting specific antibody later in life, and 2'-mercaptoethanol treatment of the cord sera did not decrease the hemagglutination-inhibition antibody titers. There was no evidence, therefore, to indicate that transplacental infection had occurred. Unfortunately, no details were provided on the severity of the maternal infections, except that in two cases clinical illness had been identified retrospectively, or on the levels of pre-existing antibody from previous infections with related strains of influenza. There have been no reports of attempts to isolate influenza virus from first-trimester fetal tissues obtained either from fatal cases of influenza or from natural or therapeutic abortions.

Transplacental transmission has been observed in Swiss albino mice after inoculation with high, lethal doses of the PR8 influenza strain by the intranasal, intraperitoneal, and intravenous routes, but only during the third trimester despite attempts to isolate virus from fetuses earlier in pregnancy (41).

It would appear, therefore, that transplacental transmission can occur during the third trimester of pregnancy. However, the only evidence has come from a fatal case of influenza, and it is possible that the concentration of virus in the blood was greater than in nonfatal cases.

Indeed, high, lethal doses of virus were necessary to demonstrate transplacental transmission in mice during the third trimester. No attempt has been made to determine whether the virus can cross the placenta during the first trimester although experiments to establish transmission at earlier stages of pregnancy in mice were unsuccessful.

LIVE INFLUENZA VACCINES—THE POSSIBLE RISK TO PREGNANT WOMEN

To be acceptable for widespread use, a live virus vaccine must satisfy a number of stringent conditions, including stable attenuation, adequate immunogenicity, and nontransmissibility. The main area of concern as a potential hazard to pregnant women is the risk of transmission from vaccinated individuals, and a remote but possible chance of a concomitant increase in virulence. There have been no convincing reports of either the spontaneous spread of live vaccines in a population or an increase in virulence following transmission to close contacts. McDonald et al. (32) reported transmission to close contacts in a clinical trial in the Royal Air Force, and we have found serological evidence of transmission between husbands, who had received live vaccine, and their wives, although this was relatively rare. No evidence of transmission has been observed in clinical trials in such closed communities as a state mental institution (9) and a monastery (3).

The most common symptom following intranasal inoculation of either live vaccine or placebo is rhinorrhoea. Virus has been isolated from some vaccinees for several hours after vaccination due to the shedding of residual virus (MacKenzie, unpublished data) and up to 4 or 5 days after vaccination as a product of mild or subclinical infections (3). In the latter case, whether sufficient virus is released to initiate infection is questionable, since transmission has not been observed in closed communities.

A slight risk of infection does exist, therefore, for pregnant women, by transmission from vaccinated individuals with whom they have close contact, such as other family members, but there is no evidence to suggest that these transmitted infections have increased virulence.

Direct infection by vaccination is also a potential hazard during the early weeks of pregnancy in women whose condition has not been diagnosed. The vast majority of live virus vaccinations are asymptomatic, rhinorrhoea being equally common among placebos in most clinical trials, and it remains uncertain whether any viremia occurs in such infections. There have been several reports of rubella vaccination under similar circumstances, where the potential risk of malformation is believed to be much higher, but adverse effects have been exceedingly rare. It would appear, therefore, that the potential risk to the developing fetus of vaccination with live influenza vaccines during early pregnancy is slight and does not constitute grounds for termination.

CONCLUSIONS

Various reports have indicated that influenza virus infections during pregnancy may lead to an increase in the incidence of specific congenital malformations, such as CNS abnormalities, cleft lip, and reduction deformities, and to an increased risk of subsequent childhood malignancies. Other investigations, however, have been unable to substantiate such claims. A comparative assessment of the evidence, both for and against, was difficult, particularly with the wide variety of methods used in compiling and classifying data, but several features emerged which were inconsistent with a direct causal relationship between maternal influenza infections and either congenital malformations or subsequent neoplasms in children.

Rubella and other known teratogens have been shown to cause patterns of congenital malformations which constituted specific syndromes, but no grouping of malformations was observed following maternal influenza infections. An increase in the incidence of CNS abnormalities was found only in Dublin and, to a lesser extent, in Finland; if such an increase represented a causal relationship, it should have been apparent in the large-scale retrospective investigations. Conversely, the increased incidence of cleft lip and reductive deformities found in the population surveys, although probably significant, was much too small to have been detected in the other studies (the increased risk being in the order of 1 in 24,000). Several environmental factors and a genetic predisposition have been shown to be important in the epidemiology of anencephaly, with some areas having a high natural incidence. The most logical explanation for the high incidence rates in Dublin and Finland, therefore, is that both are areas with a high, or potentially high, natural incidence and that the increase in incidence observed shortly after influenza epidemics is due to a stimulation by an unknown factor which may or may not be influenza. However, since most studies ascertained influenza infections by self-diagnosis, only severe infections would have been remembered, and

other possible factors such as hyperthermia and various drugs cannot be discounted.

The results which indicated a putative association between maternal influenza and subsequent childhood malignancies are equally inconsistent. In one study, a large increase in the incidence of neoplasms of lymphatic and hematopoietic tissue was observed in children born during a single week following the 1957 Asian epidemic, and a similar trend was found after other epidemics. This finding for the 1957 epidemic was supported by a study in Finland, although the incidence rates were substantially lower, but an increased incidence was not observed after other influenza epidemics. In a third investigation, a small increase in incidence was found for all neoplasms, with no particular type predominating. Thus, conflicting results were obtained in all three reports. A fourth study was unable to detect an increased incidence at any period following six epidemics. No explanation for these anomalous results is readily available, but they provide little evidence to suggest a causative role for influenza.

It would appear from the available data, therefore, that probably no direct association exists between maternal influenza infections and either congenital malformations or subsequent neoplasms during childhood. No investigation, however, has been made in sufficient depth to verify this conclusion, and a large prospective study is urgently needed to provide a proper assessment of the putative hazards. This could best be undertaken in an area with a relatively stable population and with recognized pediatric and maternity hospital facilities. It is interesting to note that, despite widespread use of live influenza vaccines in Yugoslavia, no increase in the incidence of congenital malformations or subsequent childhood malignancies has been observed (Ikic, personal communication).

The widespread use of live influenza vaccines, on the basis of the above conclusions, should present little risk to the fetus in terms of congenital malformations or subsequent childhood leukemia, either by transmission from vaccinated individuals or by accidental vaccination in women whose pregnancy has not been detected. Nevertheless, precautions similar to those employed in rubella vaccination would be advisable until more information becomes available.

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