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ASIAN INFLUENZA IN PREGNANCY AND CONGENITAL DEFECTS

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Influenza caused by the Asian strain of virus A first became epidemic in Great Britain in the latter half of the year 1957. Available statistics show that it spread rapidly and widely, affecting the southern parts of the country rather later than the northern. Most of the strains isolated from patients throughout the country were shown to be of the Asian variety (McDonald, 1958; Ministry of Health, 1960).

In a detailed inquiry into its incidence in a general practice situated on the south-eastern outskirts of London (Woodall, Rowson, and McDonald, 1958), it was shown that the epidemic in that area lasted about 8 weeks, that the main incidence lay between mid-September and late October, and that the peak was reached in the week ending October 13. About one-third of persons of all ages, children as well as adults were recorded as attacked, and it was concluded, from a comparison with national insurance statistics, that this prevalence was not unlike that for the country as a whole. In particular we may note from this local investigation that of 253 women in the childbearing age group of 15–39 years, influenza was diagnosed in as many as 28 per cent. Under such conditions as these the opportunity was taken to investigate the possible effects of this new (or renewed) influenza virus upon the foetus when the illness concerned a woman in pregnancy.

ASCERTAINMENT OF CASES.—To identify such women, who during their pregnancy suffered an attack of influenza, all those who attended the antenatal clinic at the Central Middlesex Hospital (North-west London) for the first time between November 29, 1957, and March 7, 1958, were specially interrogated by an almoner wholly employed and experienced in medical research. The date of her last mentrual period having been recorded, each woman was asked whether since the summer of 1957 she had been ill with influenza, and if so, the dates of the attack. If she said she had had influenza, three further questions were asked:

(*a*) Whether she had had a temperature;

(*b*) Whether she stayed in bed;

(*c*) Whether she consulted a doctor.

If she had consulted a doctor, a letter was sent to him asking whether in his opinion the illness referred to appeared likely to have been influenza. There could, of course, be no evidence that any such illness was due to the Asian strain of virus but it is known, as already stated, that the epidemic at this time was in general due to it.

Of 661 women interviewed in this way, 240 (36·3 per cent.) said that they had had influenza. Of these 240 cases relevant to the investigation, 65 were excluded from further observation for the following reasons:

(*a*) Three subsequently proved not to be pregnant;

(*b*) Twelve aborted (naturally or induced);

(*c*) Fifty were referred elsewhere for the supervision of their confinement and passed outside our observation.

We have, therefore, particulars of the infants born to 175 women delivered in the Central Middlesex Hospital. (Two bore twins so that the number of babies involved is 177.)

Not all these 175 women, however, were regarded as having suffered an attack of influenza. In accordance with the criteria mentioned above, they may be divided as in Table I, which shows that 128 were accepted as having had influenza (though it is likely that some did not) and 47 were not accepted (though it is possible that some did have influenza). The attack rate of 128 in 606 women (21 per cent.) is of the same order as the 28 per cent. reported by Woodall and others (1958) in S.E. London.

TABLE I

ASCERTAINMENT OF 175 POSSIBLE CASES OF INFLUENZA DURING PREGNANCY

Nature of Evidence regarding Influenza	Number of Cases
(*a*) Diagnosis confirmed by doctor who saw the patient during the illness	49
(*b*) Doctor called in during illness but kept no rrecod of the case (22 cases) or did not reply to letter of inquiry (27 cases)	49
(*c*) Mother's statement that she had a temperature or stayed in bed	30
Total accepted as influenza	128
(*d*) Diagnosis not confirmed by doctor who saw the patient during the illness	40
(*e*) Mother had not had a temperature no rstayed in bed	7
Total not accepted as influenza	47
Total	175

The 177 infants subsequently born to these women were all specially examined for congenital defects by one of us (J.S.). The inquiry thus meets the requirements of a prospective investigation.

In analysing the results we have followed the normal obstetric procedure of calculating the stage of pregnancy at which the illness took place from the first day of the last preceding menstrual period.

RESULTS

The results of the inquiry are set out in Tables II to V.

Of the fifty infants born to women whose attack of influenza had been medically confirmed two showed abnormalities (Table II), in one case a hare lip and extensive naevus of the face, and in the other an extra digit attached to a finger. In both instances, however, the influenza attack had *preceded* the pregnancy—by as much as 2 months in one instance and by 2–3 weeks in the other (Table IV, opposite). Of the 22 infants whose mothers had had influenza during the first trimester of their pregnancy, none had defects and none was stillborn.

Turning attention to the group of women whose attack had not been medically confirmed, there were, it will be seen, 41 whose illness took place in the first trimester. Of the babies subsequently born to them one was stillborn and two had defects: *viz.* one case of hypospadias following influenza in the first week or two of pregnancy and one infant who died soon after delivery with a diagnosis of congenital heart lesion and ? cerebral haemorrage following influenza at about the 11th–12th week of pregnancy. There was also one woman with a stillborn child whose attack preceded the start of pregnancy by about 2 weeks (Tables II and IV).

Looking finally at the group of 48 infants born to women whose illness was not accepted as influenza, there was one who had a stillborn child and whose illness preceded the pregnancy. Of the thirty women in this group whose illness took place during the first trimester none had a stillborn and none a defective child (Tables III and IV, opposite).

In short, there is no clear evidence in these data of congenital defects following the Asian influenza during pregnancy. Taken at its worst there were

TABLE II

OBSERVATIONS ON CASES ACCEPTED AS INFLUENZA

Stage of Pregnancy at which Influenza Commenced	Nature of Evidence of Influenza in Mother					
	Confirmed by Doctor			Mother's Statement		
	No. of Children	No. Stillborn	No. Liveborn with Abnormality	No. of Children	No. Stillborn	No. Liveborn with Abnormality
Before Last Menstrual Period	17	0	2(*a*, *b*)	23	1(*c*)	0
Weeks of Pregnancy: 1st– 4th	10	0	0	13	0	1(*d*)
5th– 8th	5	0	0	14	0	0
9th–12th	7	0	0	14	1(*e*)	1(*f*)
13th–16th	6	0	0	10	0	0
17th or Later	5*	0	0	5	0	0
Total	50*	0	2	79	2	2

* Including one pair of fraternal twins For *a*, *b*, *c*, *d*, *e*, *f*, see Table IV

TABLE III

OBSERVATIONS ON CASES NOT ACCEPTED AS INFLUENZA*

Stage of Pregnancy at which Influenza Commenced	No. of Children	No. Stillborn	No. Liveborn with Abnormality
Before Last Menstrual Period	7†	1(*g*)	0
Weeks of Pregnancy 1st– 4th	10	0	0
5th– 8th	9	0	0
9th–12th	11	0	0
13th–16th	7	0	0
17th or Later	4	0	0
Total	48†	1	0

* The seven cases where the mother's statement was not accepted (see Table I) lie as follows: one at 1st–4th, one at 9–12th, two at 13–16th, three at 17th or later.
† Including one pair of fraternal twins.
(*g*) See Table IV.

63 women who had "accepted" influenza during the first trimester and two of their infants had defects. On the other hand, there were 66 women who had "accepted" influenza either before their pregnancy commenced or in the 2nd or 3rd trimester and again two of their infants had defects (both of which occurred in the "preceding pregnancy" group). An alternative comparison we can make is between (*a*) the two defective babies in 89 born to mothers whose influenzal attack took place during pregnancy, an incidence of 2·2 per cent., and (*b*) a general figure for congenital malformations (excluding minor blemishes) found in all infants born alive in the same hospital from a special count made some years earlier (in 1953), namely 27 in 1,996 livebirths or 1·35 per cent.

In Table V we have examined the data from the point of view of birthweight. The only contrast of interest within these data appears to be between the 89 women with "accepted" influenza during pregnancy, amongst whom there were eight infants weighing 5½ lb. or less (9 per cent.) and the 41 women with "not accepted" influenza during pregnancy, who had only one such baby (2·5 per cent.). The difference is not, however, statistically significant and it may also be noted that amongst the 47 women whose illnesses *preceded* pregnancy there were four babies of 5½ lb. or less (8·5 per cent.). The mean birth weight of the babies born to mothers who had influenza during pregnancy was 7 lb. 0 oz. compared with 7 lb. 6 oz. for those whose illness was not accepted as influenza and 7 lb. 3 oz. for sixty babies born to mothers who had either chicken pox, mumps, or measles during pregnancy (Hill, Doll, Galloway, and Hughes, 1958). The differences are clearly slight.

TABLE IV

DETAILS OF STILLBIRTH AND CONGENITAL DEFECTS

Reference* (and Stage of Pregnancy)	Start of Last Menstrual Period	Onset of Influenza	Date of Delivery	Child		
				Sex	Birth Weight lb. oz.	Condition
a (Before)	10.11.57	Mid-Sep ., 1957	26.8.58	F	5 6	Hare lip and extensive naevus left side of face.
b (Before)	3.10.57	15.9.57	6.7.58	M	6 9	Extra digit attached to right fifth finger.
c (Before)	10.11.57	End Oct., 1957	3.9.58	M	8 2	Stillborn, difficult delivery, cord round neck
d (1–4) week	13.11.57	23.11.57	9.9.58	M	8 15	Hypospadias.
e (9–12) week	24. 8.57	End Oct., 1957	31.5.58	?	?	Macerated foetus, died in utero
f (9–12) week	9. 9.57	Near end of Nov., 1957	8.4.58	M	3 8	Died after 8 hrs, *post mortem* refused. Diagnosis, congenital heart-lesion, ? cerebral haemorrhage.
g (Before)	15. 9.57	August, 1957	15.6.58	M	?	Stillborn, Caesarean section after failed forceps, birth injuries.

* In references (*a*) to (*f*) the illness in the mother was accepted as influenza; in (*g*) it was not.

TABLE V

MEAN BIRTH WEIGHTS OF LIVEBORN CHILDREN

Stage of Pregnancy at which Influenza Commenced	Cases with Diagnosis Confirmed by Doctor lb. oz.	Cases Based on Mother's Statement lb. oz.	All Cases Accepted as Influenza lb. oz.	Cases not Accepted as Influenza lb. oz.
Before Last Menstrual Period..	7 4 (1)	6 14 (2)	7....0 (3)	7 4* (1)
Weeks of Pregnancy 1st–4th	7 2	7 7 (1)	7 5 (1)	7 9
5th–8th	7 6	6 6 (3)	6 11 (3)	7 14
9th–12th	6 6 (1)	7 5 (2)	7 0 (3)	7 3
13th–16th	6 8 (1)	7 4	6 15 (1)	7 7
17th or later	6 13*	7 1	6 15*	6 8 (1)
All Periods	7 0* (3)	7 0 (8)	7 0* (11)	7 6* (2)

* Including one pair of fraternal twins. Figures in brackets indicate number of infants weighing 5½ lb. or less at birth.

Discussion

The negative findings of this present small inquiry are in contrast to those reported by Coffey and Jessop (1959) who studied women exposed to this same epidemic of Asian influenza in Dublin. Of 663 births to women who, in reply to questioning at ante-natal clinics, said that they had had influenza, 3·6 per cent. were malformed compared with only 1·5 per cent. in 663 paired controls without influenza. The excess malformations were serious, for almost all affected the central nervous system, anencephaly being the most frequent. In addition, their incidence was clearly related to the trimester in which the influenza occurred, the percentage rates being 7·4, 4·3, and 2·0. As in the present inquiry, there was no evidence of an increase in the frequency of births of low birthweight.

Some slight support to these observations in Dublin is given by a study reported by Pleydell (1960) from the County of Northamptonshire. From a questionnaire sent to all midwives practising in the County, 43 pregnant women were identified as suffering from Asian influenza (the mothers "suffered from a febrile illness with symptoms and signs similar to influenza during the time when the Asian influenza reached epidemic proportions in the County"). After the baby was born the midwives' ante-natal records and Health Visitors' birth inquiry cards were checked for abnormalities, and where an abnormality was recorded its nature was obtained from the records of the general practitioner concerned, from death certification, or from hospital records. By these means three abnormalities were found compared with fourteen in the 1,040 births to mothers who were pregnant while the Asian influenza was prevalent but who were not reported as having been attacked. The three abnormalities were a case of hydrocephalus amongst twelve births following influenza in the first trimester, a case of congenital heart disease amongst eighteen births following influenza in the second trimester, and a case of spina bifida and hydrocephalus amongst thirteen births following influenza in the third trimester. These figures show no trend in relation to the time of attack though taking also into account two abortions and an infant death attributed to broncho-pneumonia the author himself concludes that "as with rubella, the risk of foetal damage appears to be greater when the illness has occurred in the early months of pregnancy".

Two studies have been reported from the U.S.A. Wilson, Heins, Imagawa and Adams (1959) measured the haemagglutination-inhibition titre against pooled Asian influenza antigen in the serum of 738 women who attended Los Angeles County Hospital for ante-natal examination between March and May, 1958. The women included in the inquiry were those in whom conception was believed to have taken place between the previous October and December, 1957, the period when an epidemic of Asian influenza first occurred in Los Angeles. Of these women, 126 were subsequently interviewed and their babies were examined. Four abnormalities were found: *viz.* two cases of anencephaly among 75 women whose sera gave positive titres, and one cleft palate and one possible amyotoria among 51 women whose sera were negative. Each of the mothers of the anencephalic babies gave a history of a cold in the third month of pregnancy, associated with a three-day fever in one case and unassociated with general symptoms in the other; the mothers of the other two abnormal children reported no illness in the first trimester. In the opinion of the authors no significant effect of Asian influenza was demonstrated.

Walker and McKee (1959) also used the haemagglutination-inhibiting titre to indicate whether the mothers had contracted Asian influenza. They, however, used several different viral antigens obtained from strains isolated from cases which occurred in Iowa city, and obtained a much higher incidence of positive results. Of 297 women who were delivered at the State University Hospital of Iowa and who were interviewed in the puerperium, 158 (53 per cent.) gave a clinical history of influenza; among these positive sera were obtained in 154 (97·5 per cent.). Positive results were, however, obtained in the whole of a further series of 101 mothers who were examined irrespective of their clinical history. Asian influenza was prevalent in Iowa from September to November, 1957, and it is presumed that all the 398 women in both series had been in contact with influenza during the first and second trimester of their pregnancy. Altogether thirteen congenital anomalies were found, including two cases in stillborn children; one of these children was anencephalic. The incidence of anomalies was slightly lower for women who had had symptomatic influenza (6/214 or 2·8 per cent.) than for women who did not report symptoms (7/184 or 3·8 per cent.). Both figures being lower than the standard incidence of 4·2 per cent. reported by Davis and Potter (1957), the authors concluded that there was no apparent alteration in incidence which could be attributed to the epidemic of influenza.

An earlier study reported by Campbell (1953) precedes the development of the Asian strain and relates to the sharp epidemic of Virus A influenza that struck a number of places in 1950/51. All expectant mothers attending certain ante-natal

clinics in Belfast (Northern Ireland), and whose last menstrual period lay between September 1, 1950, and January 31, 1951, were asked whether they had suffered from influenza (defined as "a febrile illness with a sharp onset, characterized by pains in the legs, back, or head, and sufficiently severe to require that the patient went to bed, the first day of the illness falling between December 15 and January 31 inclusive."). Following influenza there were 164 births, and as controls, with no reported influenza, there were 825 births. The stillbirth rates were 2·4 and 1·5 per cent. respectively, and of the livebirths four and seven (2·5 and 0·9 per cent.) had abnormalities. In relation to the month of pregnancy in which influenza occurred, the numbers of livebirths and deformities were as follows:

1st month 35 No deformities;
2nd month 39 One clubfoot, one hydrocephalic;
3rd month 45 One absence of kidney;
4th month 41 One clubfoot.

The numbers are small but again there is no evidence of a trend. Amongst the stillbirths there was one with anencephaly following influenza, but in the non-infected mothers there were also three such cases, together with one of spina bifida and one described as "I.V.D.".

In all these inquiries (including our own) there is, it will be noted, no laboratory evidence to confirm the clinical diagnosis of influenza. We ourselves endeavoured to check the accuracy of the mother's history by reference to the medical attendant and as a result of the replies we removed a quarter of our cases from the influenza category.

In the studies from the U.S.A. the diagnosis was based on the discovery of a positive serum reaction some time after the infection was presumed to have occurred, and it is clear from one of these that a positive reaction was common in the absence of a clinical history of any illness. It is evident, therefore, that no series provides a clear-cut comparison between mothers infected at an early period of pregnancy and mothers who were not infected or were infected only at a different period. Any difference observed between the defined groups is likely to be less than the real one as a result of the inclusion of cases not due to the influenza virus in the influenza series and of true influenzal infections in the control series. Nevertheless, if the influenza virus is capable of bringing about a congenital malformation in the foetus, it should be possible to detect this by showing that the malformation rate among children of infected mothers is higher than that normally encountered in the same area. One can, moreover, rely on there being a high probability that the majority of reported cases will in fact be influenza *when the disease is sharply epidemic*, and a comparison between mothers who report infections at different periods of pregnancy at that time should reveal a difference in the effect on the children. Judged by these criteria, our own data certainly do not suggest any appreciable hazard, since the 63 attacks occurring in the first trimester of pregnancy and the 66 attacks in a later stage of pregnancy or before the last preceding menstrual period were both followed by one stillbirth and two cases of congenital abnormality. In total, these figures are not unlike those that we reported as following mumps, chicken pox, or measles, where sixty cases of such illnesses during pregnancy were succeeded by three stillbirths and two defective infants.

If, however, the hazard was small, it would be difficult to detect by this method unless very large numbers of children were examined. In these circumstances, an indication might be obtained from national vital statistics, by seeing if there was any temporal relation between the occurrence of an epidemic and the recorded incidence of malformations. Data for the number of stillbirths due to congenital malformations are published separately for each month by the Registrar-General for Scotland, and his figures for the ten years 1950–59 (Table VI, overleaf) show that the numbers of stillbirths attributed to anencephaly in 1958 and in 1959 were above the average for the preceding 8 years; in fact, the stillbirth rate due to anencephaly was greater in both these years than at any other time since 1939, when these data began to be published. In contrast, there was no increase in 1958 and 1959 in the stillbirth rate due to other malformations. It may be noted that this latter rate was below average in both these years; but it is hardly reasonable to suppose that the recorded increase in anencephaly is an artefact due to changes in the standards of diagnosis. The increase in the number of stillbirths due to anencephaly in 1958 occurred principally in the eight months May to December, when the number was 39 per cent. above average; in the first four months of the year the increase was only 3 per cent. above average. Figures for the total numbers of births are not available by month, but the quarterly figures for 1958 show that the total numbers of births in Scotland were 6 per cent., 2 per cent., 1 per cent., and 11 per cent. above the average for the first, second, third, and fourth quarters in 1950–57, respectively. According to Grist (1959), serological tests showed evidence of influenza infection in Glasgow between August, 1957, and April, 1958, with peaks in September to October and

TABLE VI

STILLBIRTHS DUE TO ANENCEPHALY AND OTHER CONGENITAL MALFORMATIONS OF THE FOETUS IN SCOTLAND, 1950–59

Cause of Stillbirth	Period	No. of Stillbirths												Rate per 1,000 Total Births
		Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Whole Year	
Anencephalus	Average 1950–57	27·0	21·0	21·9	22·0	17·5	19·4	19·5	20·3	19·8	22·4	22·9	27·1	260·6	2·74
	1958	31	27	18	19	30	32	21	33	24	34	26	35	330	3·24
	1959	31	31	18	30	27	27	32	16	17	25	29	24	307	3·02
Other Congenital Malformations	Average 1950–57	22·8	19·3	19·5	19·1	24·0	16·8	17·5	18·6	17·9	16·5	19·1	20·3	231·3	2·43
	1958	28	15	25	5	8	18	21	14	12	16	22	24	208	2·04
	1959	15	21	19	19	12	12	18	8	14	15	19	16	188	1·85

January to March. The 1958 stillbirth data may, therefore, be regarded as fitting in with the concept that there is a small risk of producing anencephaly in the feotus, if the mother contracts Asian influenza during the first two months of pregnancy. In 1959, the excess number of stillbirths due to anencephaly was practically limited to the four months April to July; in this period the number was 48 per cent. above average, whereas in the remaining eight months it was only 5 per cent. above average. Data are not at present available to us to show whether there was any serological evidence of fresh infection in Scotland during this period.

In the light of all the evidence, the most reasonable conclusion would appear to be that anencephaly may be produced if the mother contracts Asian influenza during the first few months of pregnancy. The extent of the hazard is, however, clearly small, and it is possible that it may be produced only when other circumstances are suitable (for example, in an area where the incidence of anencephaly is normally high).

SUMMARY

Following the introduction into Great Britain of the Asian strain of influenza virus A, and the epidemic that it caused in the latter half of the year 1957, steps were taken to identify women who had suffered an attack during their pregnancy. Special observations were then made of 177 infants subsequently born to (*a*) 88 women whose influenzal attack took place during their pregnancy, (*b*) forty women whose influenzal attack preceded their pregnancy, and (*c*) 47 women whose attack was not regarded as one of influenza.

No hazard to the foetus was detected in those cases in which the illness fell within pregnancy, or, in particular, in its early stages. A positive effect has been reported in some other studies and an increase in the stillbirth rate due to anencephaly has been recorded in Scotland in 1958 and (to a lesser extent) in 1959. It seems probable that infection of the mother with Asian influenza during the early months of pregnancy can increase the risks of anencephaly, but that the extent of the hazard is normally small.

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