Congenital Defects in a Year of Epidemic Rubella*

R. E. OBER, M.D., R. J. M. HORTON, M.D., AND ROY F. FEEMSTER, M.D., DR.P.H., F.A.P.H.A.

Epidemiologists and Director, Division of Communicable Diseases, Massachusetts Department of Public Health, Boston, Mass.

A SUPPOSEDLY benign disease suddenly assumed much more serious aspects, when Gregg[1] in 1941 first reported the relationship between rubella in the pregnant woman and congenital defects in infants. As evidence accumulated, a number of serious congenital defects appeared to be directly attributable to the occurrence of rubella in pregnancy. The Australian cases reported by Gregg and others occurred following a large outbreak in 1940 in an area where the prevalence of rubella had been low for a number of years. The accumulation of a large number of susceptible adults resulted in many pregnant women becoming afflicted simultaneously. Realizing that this same situation might be occurring in Massachusetts, but unrecognized because of its relative infrequency, a survey was planned to determine if such anomalies appeared to be resulting from rubella in this state.

SURVEY METHODS

The first step in this investigation was to send letters describing the problem to eighty well known specialists in the following fields: obstetrics, pediatrics, ophthalmology, and otolaryngology. All were asked whether they had observed in their practice specific defects in the new-born such as had been previously described, and which could be attributed to rubella in the pregnant woman. Replies were received in the affirmative from six of these specialists enumerating a total of 10 such cases. Although only a few cases were thus discovered, it was felt that the problem warranted further study.

The second and most important phase of the study was an attempt to analyze the problem from a statistical viewpoint. The year 1943 was selected for such a study for several reasons: Nearly 35,000 cases of rubella had been reported to the department during that year, nearly twice the usual incidence; it was recent enough for individual memories to recall important facts; the children would be old enough for the anomalies to have been recognized at the time of the study.

The approximate number of females who had rubella in Massachusetts in 1943 was estimated from the list of reported cases for that year. It was found that 5,085 females in ages 15–49 inclusive had rubella in 1943. Since only 1 per cent of girls 15 and 16 are married in Massachusetts, the omission of those under 17 decreased the number to be surveyed to nearly 3,000. A complete list of the females in the age group 17–49 was compiled from the original report cards sent in daily from local boards of health.

* Presented before the Epidemiology Section of the American Public Health Association at the Seventy-fourth Annual Meeting in Cleveland, Ohio, November 12, 1946

The notification of communicable diseases from the various communities in the state list the name, address, age, and sex of the individual so reported. Marital status is not usually given. Accordingly, our list of adult female cases contained no information regarding marital status. Realizing all of the difficulties which would be encountered in seeking information from these individuals, various approaches to the problem were attempted. First, four communities were selected which have large, active health departments, cooperating closely with the State Department. They were asked to investigate the cases listed for their communities. This did not prove to be a satisfactory method even in these communities because of the lack of properly trained personnel who could devote the necessary time to the problem. It would have been even less satisfactory in the smaller cities and towns in the state. A brief trial of collecting information personally by departmental employees disclosed that the method was too time-consuming. The only practicable method seemed to be to canvass the group by mail.

A small pamphlet was prepared describing in simple understandable terms the purpose of the survey and the reason for requesting the information. This pamphlet was mailed to each woman on the list, and a return postal card was enclosed which was to be filled out and returned to the department. Each postal card was marked with a code number corresponding to the name of the woman in our file, so that she could be identified without signing the card. The first question on the card asked if the woman was married at the time that she had rubella in 1943. If the answer was negative, the remaining questions were not to be answered. As might be expected, some who did not read the pamphlet and card carefully became irate and wrote sarcastic replies. Fortunately, the vast majority who replied appeared to have understood the purpose of the card, and filled it out satisfactorily. A second card was enclosed to be given to an acquaintance who had had rubella while pregnant, if any such cases were known. This card, of course, had to be signed and returned to the department in an envelope. A follow-up letter was sent out at a later date to those women who failed to respond to the first questionnaire.

As a third step in the investigation, a letter was sent to approximately 6,000 physicians in the state, and to several institutions for the care of defective children, asking for information that they might have on rubella during pregnancy. Since rubella is not well reported, it was thought that some unreported cases of the disease during pregnancy might be found in this way and that information might be obtained in regard to women who did not reply to the questionnaire. This portion of the survey is not yet completed.

RESULTS OF THE SURVEY

Table 1 shows the response to the survey by mail of the reported cases in females. No questionnaires were sent to women who were obviously college or nursing students or inmates of institu-

TABLE 1

Response to Questionnaire Regarding Rubella in Pregnancy Sent to Women Ages 17–49

Massachusetts, 1946

German Measles in females 17–49		3,068
Questionnaire not sent	234	
Not located	45	
No reply	1,625	
Total		1,904
Replied to Questionnaire		1,164
Error in reporting	19	
Not married	658	
Married but not pregnant	438	
Pregnant at time of infection	49 *	
Total		1,164

* Five other cases revealed by supplementary methods

TABLE 2

Cases of Rubella in Pregnancy Revealed by Mail Survey in Females Ages 17–49 Massachusetts, 1946

Case No.	*Year Reported*	*Month of Pregnancy*	*Defects in Child*	*Remarks*
1	1941	1	bilateral cataracts microcephaly	
2	1943	1	bilateral cataracts heart lesion	
3	1943	1	?	Aborted at 4½ months
4	1943	1	?	Aborted at 3 months
5	1943	1	none	
6	1943	2	none	
7	1943	2	?	Stillborn at term
8	1943	2	heart lesion	
9	1943	2	bilateral cataracts heart lesion	Term birth (wt. 3 lbs. 12 oz.)
10	1943	2	none	
11	1943	2	none	
12	1943	2	none	
13	1943	2	?	Stillborn at about 7 mo.
14	1935	3	deafness	
15	1943	3	none	
16	1943	3	none	
17	1943	3	?	Aborted at about 4 mo.
18	1943	3	none	
19	1943	3	none	
20	1943	3	none	
21	1943	3	none	
22	1943	3	?	Aborted during 3d month
23	1943	4	none	
24	1943	4	none	
25	1943	4	?	Aborted during 4th month
26	1943	4	none	
27	1943	4	feeding problem	
28	1945	5	none	About 2 months premature
29	1943	5	none	
30	1943	5	none	
31	1943	5	none	
32	1943	5	none	
33	1943	5	none	
34	1943	5	none	
35	1943	5	none	
36	1945	5	none	
37	1943	6	none	
38	1943	6	none	
39	1943	6	none	
40	1943	6	none	
41	1943	6	none	
42	1943	6	alternating strabismus	
43	1943	7	none	
44	1943	7	none	
45	1943	7	none	Stillborn at term (autopsy)
46	1943	7	none	1 month premature
47	1943	7	none	
48	1943	7	none	
49	1946	7	none	
50	1943	8	?	Stillborn during 8th month (no autopsy)
51	1943	9	none	
52	1943	9	none	
53	1943	?	heart lesion	
54	1943	?	none	

tions. This eliminated 234 names from the list. Of the 2,834 women to whom the questionnaire was sent, 1,164 (41 per cent) replied. Replies from the original questionnaire totaled about 25 per cent, the remainder being elicited by the follow-up letter. The errors in reporting were mainly in age or diagnosis.

Of the 1,164 women who responded

to the questionnaire, 438 (38 per cent) were married at the time of their infection; 49 (11 per cent) of those who were married were pregnant when they had rubella. In addition, 5 cases of rubella in pregnancy which occurred in years other than 1943 were brought to our attention; 2 were sent to us by local health departments, and 3 responded to the second questionnaire card mentioned above.

The 54 cases discovered in this portion of the investigation are presented in Table 2. We are unable to account for the small number of cases which were reported in the last 2 months of pregnancy.

The congenital defects reported in cases 1, 2, 6, 8, 9, and 53 are typical of those previously reported as following maternal rubella. The defects listed for cases 27 and 42 are both commonly found in infants, and their relationship to the maternal infection might be questioned. We have included them in this table as defects for several reasons: Swan, et al.[4, 5, 6] have reported several cases of defective infants following maternal infection in the second trimester of pregnancy; the same authors have reported strabismus among the defects found in their cases; several authors have mentioned the occurrence of feeding problems among their cases. No defects were found in this series following maternal infection in the last trimester.

In Table 3, it will be seen that, of the 5 women who had rubella during the 1st month of pregnancy, 2 aborted, 2 had defective infants, and 1 infant was normal; thus 80 per cent of the infants were either lost or defective. In the 2nd month, 2 infants were stillborn, 2 were defective, and 4 were normal, or 50 per cent were lost or defective. In the 3rd month, 2 aborted and 1 was defective, with 6 infants normal, or one-third of the infants lost or defective. In the 4th month, there were 1 abortion and 1 defective child, with 3 infants normal; an incidence of 40 per cent lost or defective. In the remainder of pregnancy there were: 1 minor defect in the sixth month; 2 stillbirths which occurred in the seventh and eighth months; 1 defective infant for which the month of pregnancy was not known. In the 54 cases, there were 8 defective infants and 9 pregnancies which terminated in abortion or stillbirth.

Only 628 replies have as yet been received to the questionnaires which were sent to physicians in the state. Of these, 39 had treated approximately 170 cases of rubella in women of childbearing age in 1943. Thirteen of these women had been pregnant at the time of their infection. Data on 4 of these cases were incomplete; 5 of the 8 cases

TABLE 3

Cases of Rubella in Pregnancy Revealed by Mail Survey in Females Ages 17–49 Massachusetts, 1946

Month of Pregnancy	*Normal Infants*	*Defective Infants*	*Abortion or Stillbirth*	*Total Lost or Defective*
1	1	2	2	4 (80%)
2	4	2	2	4 (50%)
3	6	1	2	3 (33.3%)
4	3	1	1	2 (40%)
5	9	0	0	0
6	5	1	0	1 (20%)
7	6	0	1	1
8	0	0	1	1
9	2	0	0	0
Unknown	1	1	0	1
	37	8	9	17 (31.6%)

TABLE 4

Cases of Rubella in Pregnancy in Massachusetts Study, Combined with Those Reported by Fox and Bortin and Aycock and Ingalls

Trimester of Pregnancy	No. of Cases	Defective Infants		Abortions and Stillbirths		Total Lost and Defective	
		No.	Per cent	No.	Per cent	No.	Per cent
First	40	13	32.5	7	17.5	20	50.0
Second	22	2	9.1	1	4.6	3	13.6
Third	14	0	...	2	14.3	2	14.3
Unknown	2	1	...	0	...	1	50.0
Totals	78	16	20.5	10	12.8	26	33.3

in the first trimester had defective infants, in 1 case there was an abortion, and only 2 infants were normal. The single case reported in the third trimester produced a normal infant.

We were disappointed that physicians failed to remember or report more cases of rubella in the second and third trimesters of pregnancy. It does not seem plausible that rubella selects women in the first trimester of pregnancy. Undoubtedly the knowledge that important defects occur during that period focused attention on those who were most likely to show abnormalities.

DISCUSSION

Although a large number of cases of congenital defects following maternal rubella have been reported, the majority of these have been discovered by investigating pregnancies which resulted in defective infants. This may have given a distorted view of the incidence of defective offspring from pregnancies during which the mother has contracted rubella. Two recent surveys have approached the problem with the purpose of determining the proportion of defective children which might be expected from such pregnancies. These surveys of Fox and Bortin [2] and of Aycock and Ingalls [3] included 15 cases. All of the defects observed were in instances in which the rubella had occurred during the first trimester of the pregnancy. Of the 11 cases which occurred in the first trimester, 3 showed defects, an incidence of 28 per cent, compared to 23 per cent in the present survey. A 4th infant was stillborn, giving a total of 6 (25 per cent) lost and defective infants, compared to 50 per cent in Table 3.

In Table 4, we have combined the 54 cases from this study, 11 cases from Fox and Bortin, and 4 cases from Aycock and Ingalls. The data are given by trimester rather than by month in order to include the largest possible number of cases. The total proportion of infants lost and defective for the three periods is: 50 per cent for the first; about 14 per cent each for the second and third. It is interesting to note in comparison that the data presented on the effects of poliomyelitis in pregnancy by Aycock and Ingalls show a somewhat similar proportion of lost and defective infants, namely, 56 per cent, 26 per cent, and 14 per cent for the three periods. However, the proportion lost by abortion and stillbirth after poliomyelitis is much higher, and the number of defectives much lower. The figures given in Table 4 for the total period of pregnancy are probably not a very close approximation to the true picture due to the small number of cases in late pregnancy. Undoubtedly, the lack of reported defects in late pregnancy causes observers to overlook instances of rubella late in the period.

With the exception of Aycock and Ingalls,[3] no previous authors have emphasized that abortions and stillbirths may result from infection of the pregnant woman with rubella. The frequent interruption of pregnancy by other more

serious diseases is well known. It is apparent from the data presented here that the interruption of pregnancy as a sequel to maternal infection with rubella is frequent enough to deserve further investigation. The number of abortions and stillbirths uncovered in our survey is as large as the number of defective children.

A definitive study of the effects of rubella and other diseases during pregnancy on the resulting child has yet to be done. Such studies would involve finding cases while the mother is ill with the disease, verifying the diagnosis and the stage of pregnancy, following the pregnancy to its conclusion, obtaining careful autopsies on all infants lost by abortion or stillbirth, and following up infants to the age of 12 to 15 years, if necessary, to catch all important abnormalities. This type of investigation would be of considerable value, but would take a number of years to complete. Meanwhile, it is necessary that estimates of the gross effects on the fetus of maternal disease during pregnancy be determined as rapidly as possible. As suggested by Fox and Bortin,[2] more surveys of this type are needed for rubella. The total of 78 cases so far reported, which have been collected on a comparable basis, give some indication of the incidence of defective infants to be expected following maternal infection with this disease. The addition of more cases from other similar surveys would greatly strengthen the inferences which can now be made. Except for poliomyelitis, no information is available as yet on the incidence of defects after other diseases, although several are known to cause such defects.

In spite of the striking incidence of abnormalities of pregnancy during the first trimester, we must be cautious in attributing a causal relationship to rubella for all the defects found in this survey. We can be sure that some of them would have occurred if the mothers had not had rubella. Comparisons are needed with outcomes of pregnancies not complicated by communicable diseases as well as with those complicated by other virus and bacterial diseases.

SUMMARY

1. The results of a survey of adult females who had rubella in 1943 to determine the effects of the disease on infants are outlined and discussed.

2. Of 54 pregnancies discovered in replies to questionnaires sent to females 17–49 years of age, infants with abnormalities were observed in 8, abortions or stillbirths occurred in 9. Eleven of the 17 abnormal pregnancies were in women who contracted rubella during the first trimester.

3. Of 9 pregnancies reported by physicians in response to questionnaires, only 3 produced normal infants. Eight of the 9 women, however, contracted rubella in the first trimester.

4. Caution should be observed in attributing all such defects in infants to rubella.

5. The need of more comprehensive surveys to determine the comparative incidence of abnormal pregnancies in other virus and bacterial diseases as well as abnormalities in pregnancies not complicated by communicable diseases is discussed.

REFERENCES

1. Gregg, N. McA. Congenital Cataract following German Measles in the Mother. *Tr. Ophth. Soc. Aust.*, 3:35, 1941.

2. Fox, M. J. and Bortin, M. M. Rubella in Pregnancy Causing Malformations in the Newborn. *J.A.M.A.*, 130:568 (March 2), 1946.

3. Aycock, W. L. and Ingalls, T. H. Maternal Disease as a Principle in the Epidemiology of Congenital Anomalies. *Am. J. M. Sc.*, 212:366 (Sept.), 1946.

4. Swan, C., et al. Congenital Defects in Infants following Infectious Diseases during Pregnancy. *M. J. Australia*, 2:201 (Sept.), 1943.

5. Swan, C., et al. Congenital Defects in Infants following Infectious Diseases during Pregnancy, with Special Reference to Rubella. *M. J. Australia*, 1:409 (May 6), 1944.

6. Swan, C., and Tostevin. Congenital Defects in Infants following Infectious Diseases during Pregnancy, with Special Reference to Rubella. *M. J. Australia*, 1:645 (May 11), 1946.