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Consequences of Natural Exposure to Rubella during Pregnancy* (32687)

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Although rubella is usually a mild disease in children or adults, the serious consequences to the fetus in the form of congenital anomalies following maternal infection early in pregnancy have led to extensive studies designed to prevent the disease during that period. Since control through artificial, active immunization, a promising likelihood in the near future, is not currently available, reliance has been placed on passive immunization with pooled lots of human gamma globulin. In spite of the known rubella antibody content of such preparations, the data on effectiveness of this procedure have been conflicting. Reduction in the incidence of clinical disease resulting from administration of gamma globulin to exposed individuals has been reported (1–6), but the lowest attack rates have clearly been related to the injection of larger quantities shortly after, or even prior to exposure. Similarly, a decreased incidence of defects in children exposed during fetal life has been correlated with earlier injection of their mothers (7). Variation in effectiveness of different lots of gamma globulin has been observed (8) and others have reported no significant effect on the incidence of infection (9, 10). It is notable, however, that subclinical infection has been demonstrated serologically in recipients of gamma globulin (6, 10) and that the incidence of viremia in a small group of inoculated subjects was found to be the same as in uninoculated controls (9, 10). These findings suggest that attempted passive immunization, while frequently suppressing clinically recognizable disease, may allow the virus to cross the placenta and damage the fetus.

This report describes the incidence of clinical and subclinical rubella with associated effects on infants in relation to the administration of gamma globulin to women exposed during pregnancy.

Materials and Methods. Paired specimens of human sera which had been collected during the second or third month of pregnancy and at the time of delivery were available as part of a larger and continuing prospective study of the etiology of congenital anomalies (11, 12). During the years 1964 and 1965, which were characterized by a marked increase in clinical rubella in the area, 347 women in the study had reported an exposure to the disease. The degree of these exposures was difficult to evaluate, especially since many had occurred prior to the first visit to an obstetrician and shortly before the collection of the first blood specimen. One hundred and twenty-nine women gave a history of such ex-

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TABLE I. Rubella Antibodies in Paired Sera from 347 Pregnant Women.

Antibodies in paired sera	Exposure in relation to first blood specimen				Total
	Before		After		
	No γ-globulin	γ-globulin	No γ-globulin	γ-globulin	
Both positive	61	38	155	11	265
Both negative	10	4	22	5	41
Increased titer	4	12	23	2	41
Total	75	54	200	18	
	129		218		

posures and 218 reported contact with a case subsequent to the first visit and during the period of observation in the study. The decision whether or not to administer gamma globulin had been made by the individual physician and was largely dependent upon the month of pregnancy in which exposure occurred. All injections were intramuscular. Various commercial lots of gamma globulin had been used and their rubella-antibody content was not known. Serum specimens from these subjects had been stored in the frozen state until tested.

The titers of rubella antibody were determined by the indirect fluorescent-antibody technique (13). The end points obtained were consistent with those resulting from the conventional neutralization test employing either interference or direct CPE. Appropriate controls were incorporated into each test.

The physical condition of each infant had been determined by an examining pediatrician at birth and again several weeks later during visits to the Well Baby Clinic. In addition, follow-up inquiries were made at 6 months and 1 year of life.

Results. Table I presents the number of women according to their antibody status early in pregnancy and at the time of delivery. It was found that 265 (76%) of the women had antibodies of equal titer to rubella virus in both serum specimens and were, therefore, already immune to the disease at the time of their exposure. None of them had experienced clinical rubella during pregnancy. Forty-nine had been injected, unnecessarily, with gamma globulin. Forty-one women had no detectable antibodies at either time. Since there was no evidence of either clinical or subclinical disease even though 32 had not received gamma globulin, it must be assumed that their state of susceptibility was not altered and that either the degree of contact was insufficient for transmission of the virus or that the illness to which they were exposed was not, in fact, rubella. An additional 41 (12%) were found to have clear-cut serologic evidence of rubella infection. A great majority of these showed conversion from negative to strongly positive antibody titers, but a small number gave evidence of subclinical infection in the presence of trace or very low titers of antibodies.

As mentioned previously, 129 of the women gave histories of exposure to a case of rubella during the first trimester and prior to visiting the physician and submission of the first blood specimen. Table II shows that 99 were found to be serologically immune. Of the 30 susceptible women, 16 had been injected with gamma globulin and rubella infection was serologically documented in 12, although only two had experienced clinically recognized disease. Among the 14 susceptible women who had not received gamma globulin only four cases occurred and these were all subclinical. Thus, 14 of the 16 cases would have been unrecognized in the absence of serologic tests.

Of the 218 women exposed after the first blood specimen, 166 were immune and 52 proved to have been susceptible. Only seven had received gamma globulin of whom two experienced actual infection, one clinical and one subclinical. Most of the remaining 45 susceptible women who were not injected prophylactically had been exposed after the first trimester of pregnancy; 23 of these be-

TABLE II. Incidence of Rubella among Women Exposed during Pregnancy.

Exposure in relation to first blood specimen	γ-Globulin	No. immune	No. suscep.	No. with rubella (serologically confirmed)	
				Clinical	Subclinical
Before (129)	10–20 ml	38	16	2	10
	none	61	14	0	4
		99	30	2	14
After (218)	10–20 ml	11	7	1	1
	none	155	45	12	11
		166	52	13	12

came infected, 12 clinically and 11 subclinically. Thus again, 12 of the 25 infections were detected only by serology.

The consequences to the fetus of serologically confirmed rubella infection in 41 pregnant women are presented in Table III. Of the 27 not receiving gamma globulin, four were exposed before the first blood specimen. None had experienced clinical disease, but one anomally followed second-month infection and one neonatal death occurred as a result of disease during the fifth month. Twelve of the 23 women exposed and infected after the first blood specimen actually experienced clinical rubella, all during the second or third trimester of pregnancy. One anomaly and one neonatal death occurred following second trimester infections.

The 14 women who had been injected with gamma globulin had all been exposed during the first trimester of pregnancy, 12 of them prior to the initial blood specimen. In most cases injections were given within 4 days of exposure but one instance of a 14-day interval was recorded. Although all had experienced serologically confirmed infection, it was clinically apparent in only three. One pregnancy terminated in spontaneous abortion during the fifth month and all other infants were healthy up to one year of postnatal life.

Discussion. The large percentage of pregnant women in the present study who were found to be immune to rubella is comparable to that described by Sever *et al.* (14) who tested pregnant women in 12 hospitals in the United States and showed that 82% had demonstrable antibodies. It is obvious, however, that knowledge of such resistance is largely unsuspected by the individuals in view of the unreliability of previous clinical histories and the frequent occurrence of inapparent infections. In the present report exactly half of the 82 women found to be susceptible contracted infections as a result of exposure and 63% of these had been unrecognized clinically. This incidence of 26 subclinical infections among the 41 serologically confirmed cases was almost double that of the 15 clinically recognizable illnesses and illustrates the predominantely silent nature of this infection among young adults.

Although the administration of gamma globulin apparently influenced the occurrence of clinically recognizable rubella, with only three cases among 23 injected in contrast to 12 in 59 uninjected susceptible women, it clearly failed to reduce the incidence of serologically confirmed infections. In fact, proportionately more infections were proven to have occurred in women receiving gamma globulin (14 of 23) than in those not injected (27 of 59). This result, however, would not have been realized without serologic tests as 11 of the 14 infections among inoculated women (78%) were subclinical as compared with 15 (55%) of the 27 uninjected. These findings support the observations of others (6, 10) that gamma globulin suppresses clinical rubella while allowing subclinical infection to occur.

The most important question, however, relates to the possible protective action of gamma globulin against damage to the fetus. In the present series only one of 14 pregnancies among women receiving gamma globulin was adversely affected, although all had

TABLE III. Clinical Outcome of Serologically Confirmed Rubella Infections during Pregnancy.

No γ-globulin (27)				γ-Globulin (14)					
Exposure				Exposure		Injected			
Relation to first specimen	Month	Clinical rubella	Outcome of pregnancy	Relation to first specimen	Month	Amount (ml)	Day after exposure	Clinical rubella	Outcome of pregnancy
Before (4)	2	—	Normal	Before (12)	1	16	1	—	Normal
	2	—	Anomalous		1	20	8	+	Abortion
	3	—	Normal		2	20	2	—	Normal
	5	—	Neonatal death		2	11	2	—	Normal
					2	12	4	—	Normal
After (23)	3	—	Normal		2	20	9	—	Normal
	3	—	Normal		2	20	6	—	Normal
	3	—	Normal		2	15	14	—	Normal
	3	—	Normal		2	20	2	—	Normal
	4	—	Normal		2	10	2	—	Normal
	4	—	Normal		2	14.5	3	+	Normal
	4	+	Anomalous		3	10	?	—	Normal
	4	+	Normal						
	5	—	Normal	After (2)	2	14	1	—	Normal
	5	—	Normal		3	14	4	+	Normal
	5	+	Normal						
	5	+	Neonatal death						
	5	+	Normal						
	6	—	Normal						
	6	+	Normal						
	6	+	Normal						
	6	+	Normal						
	7	—	Normal						
	7	+	Normal						
	7	+	Normal						
	8	+	Normal						
	9	—	Normal						
	9	+	Normal						

been exposed and proved to be infected during the first trimester—the period of greatest risk to the fetus. This one exception was an abortion at 5 months subsequent to clinical disease during the first month of pregnancy with onset only 2 days after gamma-globulin injection. In contrast, the consequences of infection in 27 women not receiving gamma globulin were two anomalous infants and two neonatal deaths in spite of the fact that all but seven were exposed and infected *later* than the first trimester. In fact, these data illustrate that damage to the fetus can occur, not only as a result of subclinical infection, but also as late as the fourth and fifth months of pregnancy.

The possible mode of action of gamma globulin in protecting the fetus in spite of infection of the mother represents a phenomenon which may be related to a reduction in circulating virus as noted by others (9). A curious and perhaps significant finding in the present study was an apparent delay in the development of antibodies in women exposed and injected with gamma globulin from 5 days to 4 weeks before the collection of the first blood specimen. Although a few of the first sera contained very low levels of antibodies most were completely negative at that time. The subsequent specimens collected at delivery were all strongly positive. No further exposures to the disease were known to have occurred. In our experience with specimens collected at intervals following clinical disease

antibodies developed rapidly during the first week after rash and reached a maximum in 14–16 days. It is, therefore, conceivable that gamma globulin administered during the first trimester, while not preventing subclinical infection, delays it beyond the period of greatest potential damage to the fetus.

Summary. Blood specimens collected early in pregnancy and again at delivery from 347 women with histories of exposure to rubella were tested for antibodies by the indirect fluorescent-antibody technique. Gamma globulin had been administered to 72 following exposure. Previous immunity was detected in 265 of the women who were found to have antibodies of identical titer in both specimens. Serological evidence of infection during pregnancy was demonstrated in 41 of the 82 women whose first sera were negative for antibodies. Twenty-six of these infections were subclinical and only 15 were recognized as clinical rubella. Gamma globulin did not reduce the incidence of infection in susceptible women, which was actually higher than in the uninjected, but markedly suppressed the development of clinical disease. Damage to the fetus following first trimester infection resulted only once among 14 pregnancies in which gamma globulin had been administered. By contrast, four of 27 pregnancies of uninoculated women terminated abnormally, even though 20 of them were infected after the first trimester. There was evidence of delayed infection following injection of gamma globulin and the possible significance of this phenomenon is discussed.

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