Papers and Originals

Gammaglobulin in Prevention of Rubella and Congenital Defect : A Study of 30,000 Pregnancies

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Gammaglobulin has been available to doctors in England and Wales since 1954 for the protection of pregnant women exposed to rubella. An analysis of results obtained during the period 1954-61 showed a reduction in the attack rates, but the more important question of whether congenital defects were also prevented could not be examined at that time (McDonald, 1963). Since then the isolation of rubella virus and the development of serological tests for antibody have enabled many aspects of the problem to be investigated with more precision. In a study of the effects of gammaglobulin on artificially induced rubella in volunteers Green *et al.* (1964) showed that serological conversion and viraemia may occur in the absence of clinical manifestations of illness. Brody *et al.* (1965) concluded from a trial among young schoolboys during an epidemic in Alaska that gammaglobulin halved the infection rate as determined serologically and reduced the clinical attack rate to about a quarter. The dosage used in this trial was relatively large—0.25 ml./lb. (0.55 ml./kg.) of body weight, presumably in 16% solution.

None of these findings is of much assistance to the pregnant woman or her doctor since they are compatible with optimistic and pessimistic interpretations. Quite modest doses of gammaglobulin may not only reduce risk of infection and clinical illness in the mother but protect the foetus should these occur; moreover, gammaglobulin might protect the foetus from other teratogenic agents. On the other hand, it has been argued that gammaglobulin may at most obscure the symptoms of rubella and do nothing to prevent viraemia or damage to the foetus, so giving rise to a false sense of security, which is worse than useless. This paper, which is mainly concerned with the outcome of pregnancy in women who have received gammaglobulin, throws some light on these questions.

Background

Between 1954 and the end of 1962 gammaglobulin was issued for 36,577 rubella contacts. The demand at first grew slowly, but an epidemic in 1958 helped to popularize its use, which thereafter was maintained at a higher level. Even so, by the end of 1960 only 9,556 doses had been issued, mostly during times of low prevalence. In 1961 the demand increased and 6,565 doses were issued; this was followed in 1962 by what appeared to be a severe and widespread epidemic (Fry *et al.*, 1962), during which 20,456 doses were distributed. The study reported in this paper is confined to the period 1956-62, during which 35,825 doses were issued.

Dosage and the types of gammaglobulin available underwent changes during the period of study. Until June 1958 the dose supplied was 750 mg., the same as that for measles; it was then increased arbitrarily to 1,500 mg., only to be reduced again to 750 mg. from June to September 1961 because of shortage. From then on 750 mg. remained the standard dose, though 1,500 mg. was supplied when the risk seemed specially high—for example, for home contacts exposed during the first eight weeks of pregnancy. As over 60 laboratories undertook the distribution of gammaglobulin and requests were considered on their merits, these trends give only a general indication of what occurred. Comparisons of the effects of dosage are therefore difficult and must be interpreted with caution.

Until 1961 all the gammaglobulin used was prepared at the Lister Institute and over half (54%) of the material used in the entire period was from that source, but after 1960 supplementation became necessary. In 1961 20% was from France, and in 1962 67% was from Holland and 9% from France. Lister gammaglobulin was prepared by the method of Kekwick and Mackay (1954) whereas the French and Dutch manufacturers used the Cohn *et al.* (1944) method of fractionation.

Methods

Information on whether or not women contracted rubella and on the outcome of pregnancy were obtained by three postal inquiries with standard questionnaire forms. The first inquiry was sent out with the gammaglobulin requesting the doctor to complete and return the form 28 days after inoculation. This form was returned for 30,764 (86%) of the doses issued during 1956-62. A substantial proportion of the remaining 14% of doses were sent back to the issuing laboratory unused; our record system did not allow for this, and the number so returned is unknown. The second inquiry, made three to nine months after the expected date of delivery, gave information on the pregnancy and the state of the baby at birth. It also confirmed whether or not rubella had occurred within 28 days of the injection or at any time subsequently. Of 30,764 forms sent out, 26,930 (88%) were returned. This form was also sent in respect of 143 women who were given gammaglobulin after the appearance of the rash in the hope of modifying the effects on the foetus; all these forms were completed.

Finally, when the children were at least 2 years of age a third postal inquiry was made about cases in which the foetus had been at greatest risk. This group comprised women known to have had rubella while pregnant, together with those who were in contact in the family during the first 12 weeks of gestation. In this inquiry the doctors were asked specifically about the presence of rubella-type defects—deafness, heart

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disease, and cataract. The third inquiry was sent in respect of 7,631 surviving children in the group at high risk and a report was received on 5,722 (75%). Most of the failures were due to the fact that the child's family had moved to a new address and could not be traced.

In addition to the three postal inquiries, 229 children whose mothers had rubella in pregnancy were selected from 360 children in this category who were reported alive at the second postnatal inquiry. The basis for selection was their proximity to a number of centres throughout the country to which they were called to be seen by one of us (C. S. P.). A complete physical examination was made with careful auditory and ophthalmic assessment; an electrocardiogram and chest x-ray film were taken when indicated. The Stycar test devised by Mary Sheridan (1958) was used for the detection of hearing defect.

Some of the least satisfactory data used in the analysis concerned the stage in pregnancy when the gammaglobulin was given. This question was not asked until the first postnatal inquiry, and by that time the doctor was often unable to supply the date of the last menstrual period. So far as possible the dates in question were estimated from available information and at worst from the date of delivery, but even this was not possible in pregnancies which ended in miscarriage.

Results

Rubella Attack Rate

Of the 30,764 women for whom there was information, 370 (1.2%) developed rubella within 28 days of inoculation and a further 97 (0.3%) at varying intervals thereafter. Table I shows that the attack rate was four times higher when the exposure to infection was in the family rather than elsewhere. Only before 1961 was there any evidence of better results with the higher dose. The attack rates increased about twofold between the early years and 1962. The reason for the increase was the high rate during the epidemic period in the first half of 1962 (Table II). The proportion attacked was highest in those given gammaglobulin immediately after exposure (Table III), but it is

TABLE I.—Rubella Attack Rates in Relation to Dose of Gammaglobulin and Type of Contact, 1956–62

Years	Dose (mg.)	Type of Contact			
		In Family		Outside Family	
		No. at Risk	Attacked within 28 Days of Exposure No. (%)	No. at Risk	Attacked within 28 Days of Exposure No. (%)
1956–60	750	1,695	20 (1.18)	1,744	5 (0.29)
	1,500	2,119	17 (0.80)	2,273	5 (0.22)
1961	750	1,114	13 (1.17)	1,137	3 (0.26)
	1,500	1,516	27 (1.78)	1,821	5 (0.27)
1962	750	7,730	195 (2.52)	6,876	42 (0.61)
	1,500	999	24 (2.40)	1,288	13 (1.01)
1956–62	750	10,539	228 (2.16)	9,757	50 (0.51)
	1,500	4,634	68 (1.47)	5,382	23 (0.43)
All*		15,173	296 (1.95)	15,139	73 (0.48)

* In addition to the 30,312 women shown in this Table, there were 452 others for whom the type of contact or dose was not recorded; one of them developed rubella, making 370 cases in all. A further 97 women developed rubella more than 28 days after exposure.

quite possible that those treated early were at greater risk. The distribution of intervals between exposure and onset of rubella when prophylaxis failed (see Chart) supports the accuracy of diagnosis in these cases. Unfortunately, it does not follow that when prophylaxis was apparently successful the diagnosis of illness in the primary case was equally accurate. Full analysis did not show any consistent difference between the results obtained with the Lister, Dutch, and French products and they have therefore been pooled. Detailed study showed that the

attack rates in older women tended to be slightly higher than in younger women, but once again they may not have been at equal risk.

TABLE II.—Rubella Attack Rates in Family Contacts by Date of Inoculation, 1956–62

Season	1956–60		1961		1962	
	No. at Risk	Attacked No. (%)	No. at Risk	Attacked No. (%)	No. at Risk	Attacked No. (%)
Jan.–Mar. ..	Not known	{	409	7 (1.71)	1,598	40 (2.50)
Apr.–June ..			945	15 (1.59)	4,489	146 (3.25)
July–Sept. ..			837	11 (1.31)	2,068	29 (1.40)
Oct.–Dec. ..			441	7 (1.59)	584	4 (0.68)
Whole year(s) ..	3,816	37 (0.97%)	2,632	40 (1.52)	8,739	219 (2.51)

The figures in this Table do not agree entirely with those in Table I because information was not complete in all cases.

TABLE III.—Rubella Attack Rates in Family Contacts in Relation to Time Between Exposure and Inoculation

Year	No. at Risk	Exposure to Inoculation (Days)					
		0–4		5–12		13+ and Not Known	
		No. at Risk	Attacked No. (%)	No. at Risk	Attacked No. (%)	No. at Risk	Attacked No. (%)
1956–60	3,816	2,414	34 (1.4)	923	3 (0.3)	479	0
1961	2,632	1,713	31 (1.8)	577	5 (0.9)	342	4 (1.2)
1962	8,739	5,271	158 (3.0)	2,040	46 (2.2)	1,428	15 (1.0)
1956–62	15,187	9,398	223 (2.4)	3,540	54 (1.5)	2,249	19 (0.8)

The figures in this Table do not agree entirely with those in Table I because information was not complete in all cases.

Frequency distribution of intervals from exposure to onset of rubella in 351 cases (97 intervals of more than 28 days and 19 of uncertain length not shown).

Women with Rubella

Only 70% of the 610 women who had rubella in pregnancy came to term. In 16% pregnancy was terminated and the remainder either miscarried or were thought subsequently not to have been pregnant (Table IV). It may be seen in Table V that 13% of the children, live-born or stillborn, were reported to have congenital defects, and in the light of the additional findings in the sample of children visited 18% is probably a better estimate. This high figure was largely accounted for by deafness and heart defects, both characteristic of rubella. There were no cases of cataract, but in only 57 (13%) of 424 pregnancies known to have gone to term was the rubella in the first eight weeks of gestation.

The congenital defects present in this series are listed in Table VI according to the stage in pregnancy that rubella occurred and the stage of the inquiry at which they were ascertained. Most of the heart disease but little deafness was discovered at the first postnatal inquiry. The detailed examinations made

TABLE IV.—*Foetal Survival in Women with Rubella in Pregnancy, 1956-62*

	No of Cases of Rubella	Untraced at First Postnatal Inquiry	Not Pregnant	Surgical Abortion	Miscarriage	Total Births (Live and Still)	Stillbirths	Stillbirth Rate
Failures of prophylaxis	467	7	33	81	31	319	7	2.2%
Mother treated with gammaglobulin for rubella	143	0	3	17	18	105	5	4.8%
All cases	610	7 (1%)	36 (6%)	98 (16%)	49 (8%)	424 (70%)	12	2.8%

Except for stillbirth rates, percentages are calculated as a proportion of the number of cases of rubella; the figures for births include twins.

TABLE V.—*Defects in Children of Women With Rubella in Pregnancy, 1956-62*

	No. of Live Births or Stillbirths at First Postnatal Inquiry	Live Births Untraced at Second Postnatal Inquiry	Children with Rubella-type Defects				Other Children with Defects	Total Children with Defects
			Deafness	Heart	Cataract	Any		
Failures of prophylaxis ..	319	33	19 (6.0%)	9 (2.8%)	0	26 (8.2%)	13 (4.1%)	39 (12.2%)
Mother treated for rubella	105	19	10 (9.5%)	4 (3.8%)	0	13 (12.4%)	4 (3.8%)*	17 (16.2%)
All cases	424	52	29 (6.8%)	13 (3.1%)	0	39 (9.2%)	17 (4.0%)	56 (13.2%)
Additional findings in sample of 229 children visited after 2nd postnatal inquiry			13 (5.7%)+	0	0	10 (4.4%)	0	10 (4.4%)
Estimated rates, using information from visits			12.5%	3.1%	0	13.6%	4.0%	17.6%

* One of these children had microphthalmia and retinopathy. † Three of these children were already known to have heart defects.

TABLE VI.—*Details of Defects in Children of Mothers with Rubella in Pregnancy, 1956-62*

Week of Pregnancy	Defect	First Post-natal Inquiry	Second Post-natal Inquiry	Visit	No. of Children with	
					Rubella Defects	Other Defects
0-8	Heart	(57) 1	(49) 2	(28) 2	1 3	10
	" and deafness ..	1	1			
	Heart, deafness, and mental defect ..				1	
	Deafness		5		5	
	Bilateral talipes ..		1			
	Pyloric stenosis ..	1				3
	Glaucoma and spasticity	1				
9-12	Heart	(126) 1	(103) 1	(67) 7	1 23	26
	Heart, renal and pyloric stenosis ..	1			1	
	Deafness	3	13			
	Mental defect ..		1			
	" deafness" and ..			1	1	
	Vitreous opacities ..		1			7
	Microphthalmia and retinopathy ..		1			
	Hydrocephaly ..	1				
	Spasticity	1				
	Renal	1	1			
13-16	Defect of diaphragm ..	1				10
	Heart	(139) 3	(120) 1	(78) 1	3 6	
	" and nystagmus, and deafness ..	1				
	Deafness					
	Anencephaly		1			
	Scoliosis		1			4
	Ptoxis					
17+ and N.K.	Pyloric stenosis ..	1				2
	Heart	(102) 1	(88) 1	(56) 2	1 2	
	" and renal ..					
	Deafness					

Defects are listed according to the stage of the inquiry that they were ascertained. Thus, for example, of the three children shown with heart defects and deafness whose mothers had rubella in the first eight weeks of pregnancy, by the second inquiry a heart defect had been noted in all of them, but only one was thought to have a hearing defect. At the visit the other two children were also found to have hearing defects.

during the visits after the second postnatal inquiry almost doubled the estimated percentage of deafness, but the additional cases were not severe and no other congenital defects were discovered at this time. About a quarter of the children whose mothers had rubella in the first 12 weeks had heart or hearing defects; the rate fell to about 10% during the next four weeks and to about 5% after the sixteenth week. It is difficult to state these risks precisely because of the changing denominators at the first and second postnatal inquiries and visit. The outcome was more favourable in pregnancies in which rubella developed in spite of gammaglobulin than in those in which it was given after onset—4.8% compared with 2.2% for stillbirths and 12.4% compared with 8.2% for rubella-type defects—but these differences have little statistical significance ($P>0.2$ for both).

Women without Rubella

Information was obtained on the outcome of pregnancy in all but 13% of the 30,297 women who were in contact with

rubella but escaped the illness. This information is summarized in Tables VII and VIII. Six per cent. aborted, 3% were thought subsequently not to have been pregnant, and the remainder gave birth to 23,931 children of which 381 (1.6%) were stillborn and 2.6% were stated to have congenital defects at the first postnatal inquiry. Despite a greater risk from rubella the stillbirth and defect rates in the family contact group were lower, if anything, than in the group with contact outside the family. Using information from the second postnatal inquiry, we estimated that the defect rate at this stage for children whose mothers had been exposed to rubella in the first 12 weeks of pregnancy was 3.6%. Of this total rate only 3.0 per thousand had hearing defects and 3.8 per thousand congenital heart disease.

TABLE VII.—*Foetal Survival in Women Who Were in Contact with Rubella in Pregnancy But Did Not Develop the Disease, 1956-62*

	No. of Women Inoculated who Did Not Develop Rubella	Untraced at First Postnatal Inquiry	Not Pregnant	Surgical Abortion	Miscarriage	Total Births	Stillbirths	
							No.	Rate
Family contacts	14,840	1,800	538	17	956	11,678	200	1.7%
Other contacts ..	15,032	1,836	397	5	866	12,055	177	1.5%
Contact not known	425	191	10	2	27	198	4	2.0%
All contacts ..	30,297	3,827 (13%)	945 (3%)	24	1,849 (6%)	23,931 (79%)	381	1.6%

Except for stillbirth rates, percentages are calculated as a proportion of the number inoculated; the figures for births include twins.

The possibility that gammaglobulin might protect the foetus from hazards other than rubella was also examined by means of data from the first postnatal inquiry. For embryological reasons the probability of any such effect would be greater the earlier in pregnancy the inoculation was given. In Table IX the outcome is analysed in relation to dose of gammaglobulin

TABLE VIII.—Defects in Children of Women Who Were in Contact With Rubella But Did Not Develop the Disease, 1956–62

Type of Contact	No. of Live Births and Stillbirths at First Postnatal Inquiry	Children with Rubella-type Defects				Other Children with Defects	All Children with Defects
		Deafness	Heart	Cataract	Any		
Family	11,678	4 (0.03%)	38 (0.33%)	0	42 (0.36%)	241 (2.1%)	283 (2.4%)
Outside family	12,055	5 (0.04%)	49 (0.41%)	1	55 (0.46%)	276 (2.3%)	331 (2.7%)
Not known	198	0	1	0	1	0	1
All contacts	23,931	9 (0.04%)	88 (0.37%)	1	98 (0.41%)	517 (2.2%)	615 (2.6%)
Family contacts in first 12 weeks of pregnancy	7,505	3 (0.04%)	20 (0.27%)	0	23 (0.30%)	156 (2.1%)	179 (2.4%)
Additional findings on 5,362 children from 2nd postnatal inquiry*		14 (0.26%)	6 (0.11%)	0	20 (0.37%)	43 (0.8%)	63 (1.2%)
Estimated total defect rates for family contacts in first 12 weeks of pregnancy by adding findings from 2nd postnatal inquiry ..		(0.30%)	(0.38%)	0	(0.67%)	(2.9%)	(3.6%)

* The second postnatal inquiry was made in respect of 7,233 surviving children whose mothers had received gammaglobulin during the first 12 weeks of pregnancy.

TABLE IX.—Foetal Survival and Defects in Women Who Did Not Develop Rubella in Relation to Dose of Gammaglobulin, and Stage of Pregnancy When Given, 1956–62

Weeks of Injection	Dose (mg.)	Live Births and Stillbirths	Stillbirths		Children with Defect		Rate/1,000 of Children with Defects by System					
			No.	Rate	No.	Rate	Central Nervous	Musculo-skeletal	Cardio-vascular	Digestive and Respiratory	Genito-urinary	Miscellaneous
First 12 {	1,500	4,746	51	1.1%	104	2.2%	8.4	6.3	2.3	4.6	2.1	2.3
	750	10,814	155	1.4%	276	2.5%	10.2	5.5	3.8	5.1	1.6	3.9
All ..		15,560	206	1.3%	380	2.4%	9.6	5.8	3.3	5.0	1.7	3.4
After 12 {	1,500	3,133	54	1.7%	68	2.2%	8.6	4.5	3.5	3.2	1.6	2.6
	750	4,179	72	1.7%	142	3.4%	15.3	7.2	4.3	4.5	2.4	3.6
All ..		7,312	126	1.7%	210	2.9%	12.4	6.0	4.0	4.0	2.1	3.1
Week or dose not known ..		1,059	49	4.6%	28	2.6%	13.2	1.9	6.6	8.5	0	1.9
All ..		23,931	381	1.6%	618	2.6%	10.7	5.7	3.7	4.8	1.8	3.2

and to whether it was given before or after the twelfth week. In terms of age distribution and type of rubella contact the four groups were closely comparable. The stillbirth rates were somewhat lower when gammaglobulin was given early, particularly in the higher dose ($P<0.05$). The defect rates also showed differences ($P<0.1$), but these seemed more closely related to dose than to time, and the pattern was not confined to any particular diagnostic groups. The analysis was carried through to a detailed consideration of over 80 specific defects; but wide variations, presumably due to chance, in even the more numerous categories, made the interpretation impossible. Frequencies for the main types of defect found at the first postnatal inquiry are set out in Table X for comparison with other

surveys and as an indication of the level of case-finding achieved in this one.

Discussion

The two questions which require an answer are: does gammaglobulin reduce the attack rate in pregnant women exposed to rubella and, if so, is her child also protected. An attack rate of 1.95% in over 15,000 women, most of whom had no past history of rubella and who were in close contact with a case in the family, usually their own child, seems a low figure, but it is difficult to estimate accurately what it would have been without gammaglobulin. In an earlier report (McDonald, 1963) based on experience before 1962 the attack rate in family contacts was 1.27%, which compared favourably with a rate of at least 3.7% for untreated women in a survey carried out by the College of General Practitioners during roughly the same period (Watson and McDonald, 1963). In 1962, however, the attack rate rose to 2.5% in treated women and to 3.25% at the height of the epidemic. A family survey might have shown a similar increase in the rates for untreated women, but there is little information on this point.

In a description by Fry *et al.* (1962) of the 1962 epidemic in a large London suburban practice about 5% of all women of child-bearing age were actually seen with rubella, and it was estimated that the true attack rate was probably half as great again. Fry (personal communication, 1966) reported that in 156 families with a case of rubella 250 women aged 17–44 were at risk and 39 (15.6%) developed the disease. The figures are quite similar to those presented by Sever *et al.* (1965) for the 1964 epidemic in the U.S.A. They reported an attack rate of 3.5% in women exposed to rubella and given gammaglobulin (15–20 ml.) compared with 12.8% for unprotected women. The evidence from controlled trials must also be taken into account. Though these have been in children and not wholly consistent (Korns, 1952), results have generally indicated a substantial degree of protection (Landon *et al.*, 1949; Grayston and Watten, 1959; McDonald, 1963; Brody *et al.*, 1965). Altogether it seems very probable that without gammaglobulin

TABLE X.—Frequency of Congenital Defects Found At or Soon After Birth in 23,931 Live-born or Stillborn Children of Women Who Did Not Develop Rubella, 1956–62

System	More Frequent Defects	No. (Rate/1,000)	Less Frequent Defects
Central nervous system and senses	Anencephaly ..	57 (2.4)	Deafness 9, microcephaly 9, epilepsy 8, blindness 7, cerebral palsy 5, neuromuscular 5, encephalocoele 3, nystagmus 2, coloboma 2, other 9
	Spina bifida ..	54 (2.3)	
	Hydrocephaly ..	50 (2.1)	
	Mongolism ..	45 (1.9)	
	Spina bifida occulta ..	15 (0.6)	
Musculo-skeletal	Mental defect ..	15 (0.6)	Exomphalos 9, diaphragmatic or hiatus hernia 8, limb 7, absent digit 7, deficient limb 6, achondroplasia 6, spine 5, chest wall 4, mandible 3, skull 3, other 6
	Talipes ..	48 (2.0)	
	Polydactyly ..	19 (0.8)	
	Syndactyly ..	12 (0.5)	
	Dislocation of hip ..	10 (0.4)	
Cardio-vascular	Ventricular septal defect	23 (1.4)	Fallot's tetralogy 9, coarctation 7, pulmonary stenosis 6, atrial septal defect 6, transposition 4, septal defect 3, aortic stenosis 3, persistent truncus 2, other 1
	Congenital heart disease (type unspecified) ..	28 (1.2)	
	Patent ductus arteriosus	11 (0.5)	
Digestive and respiratory	Small gut 6, rectal atresia 6, oesophageal atresia 5, megacolon 4, lung 4, ano-rectal 3, tracheo-oesophageal fistula 2, other 10		Genital 9, tumour 9, gross foetal 6, fibrocystic disease 6, renal pelvis 5, cretin 3, blood dyscrasia 4, ichthyosis 2, other 12
	Pyloric stenosis ..	48 (2.0)	
	Cleft palate ..	29 (1.0)	
Other	Hare-lip ..	20 (0.8)	
	Large haemangioma ..	22 (0.9)	
	Hypospadias ..	20 (0.8)	
	External ear ..	16 (0.7)	
	Kidney ..	10 (0.4)	

The figures shown give the number of children with the specified defect whether or not other defects were also present.

the attack rate in pregnant women would have been substantially higher than it was.

The absence of an excess of rubella-type defects in the children of women who escaped rubella is more certain. The estimated rates per thousand for the children of family contacts in the first 12 weeks of pregnancy—deafness 3.0, heart defects 3.8, and cataract 0—seem to be within normal limits. Comparable figures, as yet unpublished, from a large prospective study of some 12,000 pregnancies conducted in Britain during the same period and using fairly similar methods of ascertainment were as follows: deafness 1.2, heart defects 4.5, and cataract 0.1. The rate for deafness was thus higher than in the normal series, but in our inquiry special emphasis was put on its detection. An additional point concerns the proportion of children with congenital heart disease who had a patent ductus arteriosus. This lesion is characteristic of rubella (Campbell, 1961), and in our series of women who contracted rubella 8 out of 13 children with heart disease had this defect. In contrast, in our series of women who escaped rubella there were only 11 cases of patent ductus in 93 cases of heart disease. These and other similar figures set out in Table XI suggest that if apparent rubella virus infections occurred they did no appreciable harm to the child.

TABLE XI.—*Patent Ductus Arteriosus as a Proportion of All Congenital Heart Disease*

Series	Description	Congenital Heart Disease		Patent Ductus Arteriosus	
		Rate/1,000 Births	No. of Cases	No. of Cases	% of Total
Current series ..	Rubella in early pregnancy	30.7	13	8	62
Manson <i>et al.</i> (1960)	Rubella in early pregnancy	26.4	15	Not stated	
Campbell (1961) ..	Congenital heart disease after maternal rubella		153	89	58
McDonald (1961)	Prospective inquiry in normal women	4.7	15	1	7
Slater <i>et al.</i> (1964)	Notified cases from general practice		About 1,282	153	12
McDonald (1966)	Prospective inquiry in normal women	4.5	50	12	24
Current series {	Rubella contact in family	4.4	44	3	7
	Rubella contact outside family	4.1	49	8	16

Summary

Reports were obtained on the result of inoculation of 30,764 women with gammaglobulin after exposure to rubella in pregnancy during the years 1956–62. The outcome was ascertained soon after the expected date of delivery in 26,930 (88%) cases, and further inquiries were made on selected samples of surviving children when they were 2 or more years of age.

In 1.95% of family contacts and 0.48% of contacts outside the family clinical signs of rubella developed within 28 days of inoculation. Without gammaglobulin these rates would probably have been substantially higher.

Of 610 women who had rubella in pregnancy only 70% came to term. About a quarter of the children whose mothers had the disease in the first 12 weeks had heart or hearing defects; the proportion fell to about 10% for the next four weeks and then to about 5%. The rates for stillbirth and for rubella-type defects were higher when gammaglobulin had been given *after* the onset of rubella than when the disease developed despite prophylaxis, but these differences could have been by chance ($P>0.2$).

There was no excess of cataract or heart disease and probably no excess of deafness in the children of women who did not develop rubella though exposed to it. Subclinical rubella virus infection either carried little risk for the foetus or did not occur often enough for any adverse effect to be detected.

A lower proportion of children whose mothers received gammaglobulin in the first 12 weeks of pregnancy were still-born (1.3% compared with 1.7%; $P<0.05$) or had congenital defects (2.4% compared with 2.9%; $P<0.1$) than of those whose mothers were injected after the twelfth week.

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