OUTCOME OF PREGNANCY IN A RUBELLA OUTBREAK IN NORTHERN IRELAND 1978-1979

by

J. H. CONNOLLY,¹ N. C. NEVIN,² D. M. SIMPSON,³ and H. J. O'NEILL⁴

Regional Virus Laboratory, Royal Victoria Hospital, Belfast.
Northern Ireland Genetics Service, Institute of Clinical Science,
Grosvenor Road, Belfast.

IN Northern Ireland, during 1978-79, there was a major outbreak of rubella. A similar outbreak affected the rest of the United Kingdom and other countries throughout the world.¹,² We have investigated the outcome of pregnancies of women who were diagnosed virologically as having rubella in the first four months of pregnancy during 1978-79. In addition, all infants born in 1978-79 and suspected of having intrauterine rubella infection, or who were conceived during 1979 and born during 1980, were tested and those who had rubella specific immunoglobulin M (IgM), were followed up.

MATERIALS AND METHODS

Where possible acute and convalescent sera were obtained from pregnant women after contact with rubella. Rubella haemagglutination-inhibition (HI) antibody was titrated in sera after removal of inhibitors with dextran sulphate — CaCl₂.³ Trypsin modified human O erythrocytes were used.⁴ Antibody titres were expressed as reciprocals. Rubella specific IgM was measured in sera by the indirect fluorescent antibody test on rubella infected VERO cells.⁵ Sera were absorbed with monkey liver powder, heat aggregated human immunoglobulin to eliminate non-specific staining due to possible rheumatoid factor in serum⁶ and protein A Sepharose (Pharmacia) to decrease interfering IgG.⁷

All infants, born in 1978, 1979, and the first 9 months of 1980, who were clinically suspected of having congenital rubella had their sera fractionated by ultra centrifugation on a sucrose density gradient⁸ and fractions containing rubella specific IgM were detected by the indirect fluorescent antibody test as above.

In pregnant women after contact with rubella, acute rubella infection was diagnosed if the acute sera had no detectable antibody ( < 10) and a four-fold or greater rise of antibody developed in convalescent sera. In women who were bled later than one week after contact and who had high ( ≥ 160) but not rising titres of rubella antibody, rubella specific IgM was measured and, if detected, indicated rubella virus infection within the previous two months.

The minimum immune titre of rubella HI antibody⁹ in this laboratory is 20 which is equivalent to at least 15 International Units per ml. of rubella antibody.¹⁰ Rubella HI antibody at a titre of 20 or higher, indicates that the pregnant woman is immune either in a routine screening test, or within one week after contact with rubella.

¹ Consultant Virologist. ² Professor of Medical Genetics.
³ Senior Medical Laboratory Scientific Officer. ⁴ Chief Medical Laboratory Scientific Officer.
RESULTS

Before the outbreak:- Between June 1973 and October 1975, sera from 1000 pregnant women attending antenatal clinics in hospital or general practice throughout Northern Ireland were tested for rubella HI antibody; 81.2 per cent had a titre of 20 or greater, and were regarded as immune.

The outbreak:- The number of pregnant women who either had a rash or who were in contact with suspected rubella and whose blood was sent to the laboratory is shown in the Figure. The peak incidence was June and July during 1978, and May during 1979. Although the number of requests dropped during the winter of 1978-79, they did not fall below pre-outbreak levels. The commonest history of contact with rubella was with a young child in the same household. There were 1229 more requests for rubella serology in pregnant women in 1979 compared with 1978. Many other blood samples from pregnant women who did not have rubella or contact were received as a result of extensive coverage of the outbreak on the news media.

Figure.

Rubella antibody requests per month from pregnant women in Northern Ireland who had a rash or contact* with suspected rubella.

*Date of contact is shown and not date of request.

Rubella in Pregnant Women

Sixty-seven women in 1978 were diagnosed by the laboratory as having had rubella. On follow-up, two were found not to be pregnant, and five could not be traced. Of the 60 remaining women, 31 had greater than four-fold rising titre of rubella antibody while 29 had raised but static rubella antibody titres with rubella specific IgM present in their sera. Thirty-two (53 per cent) women were recorded as having had a rash. In 1979, 108 women were diagnosed by the laboratory as having had rubella. On follow-up, 11 were found not to be pregnant, and seven could not be traced. Of the 90 women remaining, 36 had greater than four-fold rising titre of rubella antibody, while 54 had raised but static rubella antibody titres with rubella
specific IgM present in their sera. Thirty-eight women (42 per cent) were recorded as having had a rash. Of the 150 women with proven rubella, the ages ranged from 16 to 40 years with a mean of 27.1 years. Geographically, 100 of these women were located in urban areas: Belfast (33), South Antrim (32), Craigavon (17), North Down (16) and Londonderry City (2).

In 1979, a 29-year-old woman had clinical rubella during the first month of gestation of her third pregnancy. Rubella specific IgM was present in her serum taken three weeks later. A female infant was born with hepatosplenomegaly and multiple congenital abnormalities which included patent ductus arteriosus, deafness, cataract, microphthalmia, and retinopathy. Rubella specific IgM was present in her serum. The mother had received Cendehill rubella vaccine eight years previously.

OUTCOME OF PREGNANCY

Table 1 shows the outcome of pregnancy. Of the 150 pregnant women with proven rubella, 69 (46 per cent) had a therapeutic abortion. Of the 81 mothers who continued their pregnancy there were 69 (85 per cent) normal liveborn infants, three apparently normal stillbirths, and nine (11 per cent) infants with congenital abnormalities. These infants were followed-up, and Table 2 details the abnormalities. All nine mothers had a history of a rash during the pregnancy. Six of the nine infants were female, and three weighed less than 2500 grams. In two infants rubella specific IgM was not detected, but the interval between their date of birth and the date of testing was 20 and 23 months, respectively. Both babies had rubella HI antibody titres of 20, while antibody titres of toxoplasma, herpes simplex virus, and cytomegalovirus were not significant. Since rubella HI antibody had persisted longer than six months after birth, they are included.

**Table 1**

| Year | Number of women with proven rubella | Induced abortion | Normal livebirths | Normal stillbirths | Abnormal infants |
|------|------------------------------------|------------------|------------------|-------------------|-----------------|
| 1978 | 67 \(^1\) (60)                     | 27               | 27               | 2                 | 4               |
| 1979 | 108 \(^2\) (90)                    | 42               | 42               | 1                 | 5               |
| Total| 175 (150)                          | 69               | 69               | 3                 | 9               |

In 1978 and 1979, 2140 and 3369 (total 5509) women were tested.

\(^1\) In 1978 5 women could not be traced, and 2 women were found not to be pregnant.

\(^2\) In 1979 7 women could not be traced, and 11 women were found not to be pregnant.

( ) = Number of pregnant women with proven rubella traced.

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### Table 2

**Abnormal Infants born to Mothers with Laboratory Proven Rubella**

| MOTHER<sup>1</sup> Gestation (weeks) | Birth weight | Sex | INFANT Clinical features |
|-------------------------------------|--------------|-----|--------------------------|
| 10                                  | 3365         | F   | Deafness                 |
| 8                                   | 3175         | M   | Systolic murmur, hepatosplenicomegaly, purpura. |
| 8                                   | 2180         | M   | Deafness, systolic murmur. |
| 8                                   | 1620         | M   | Fallots tetralogy, hepatosplenicomegaly, osteitis. |
| 14                                  | 3310         | F<sup>2</sup> | Generalised erythematous rash; Click right hip. |
| 4                                   | 2400         | F   | Deafness, cataract, microphthalmia, and retinopathy, patent ductus arteriosus, hepatosplenicomegaly. |
| 7                                   | 3340         | F<sup>2</sup> | Large interior fontanelle, bronchiolitis. |
| 7                                   | 3005         | F   | Chest infections.        |
| 6                                   | 3062         | F   | Right cataract.          |

<sup>1</sup> All 9 mothers had a history of rubella in pregnancy.

<sup>2</sup> Rubella specific IgM negative but rubella HI antibody present.

**Abnormal infants with rubella specific IgM born to mothers not tested during pregnancy**

A further nine infants with rubella specific IgM born to mothers not tested during pregnancy were identified from sera sent to the Regional Virus Laboratory because congenital rubella was suspected in the infant (Table 3). Of these mothers, three had no history of rubella during pregnancy, and of the other six mothers, five had had a rash during pregnancy. The remaining mother had been in contact with rubella and had received human immunoglobulin. The abnormalities in the nine infants are detailed in Table 3. Five of the 9 infants were female and 4 weighed less than 2500 grams.

**Congenital rubella infants**

A total of 91 infants were tested for rubella specific IgM either because they had been born to women with proven rubella during pregnancy, or because congenital rubella was suspected in the neonatal period. Eighteen infants had rubella specific IgM in their sera. Two of these infants born in the first five months of 1978 were excluded from the study since they were infected *in utero* before the rubella outbreak, and 2 affected infants who only had rubella HI antibody, 20 and 23 months after birth, were included. Of the 14 mothers who had a history of clinical rubella, one mother had a history in the first month of pregnancy, 9 in the second month, 3 in the third month, and 1 in the fourth month. Of the 18 infants with congenital rubella infection, at the time of follow-up, 7 had deafness, 7 had a skin rash, 7 had congenital heart disease, 5 had hepatosplenicomegaly, 4 had congenital cataract, 2 had osteitis, and one had microcephaly. Two infants presented only with chest infections and bronchiolitis. One infant with hypospadias and a bifid scrotum, had Klinefelter's syndrome (47,XXY). His mother had been in contact with rubella at 8 weeks gestation and had received human immunoglobulin.
### TABLE 3

*Abnormal Infants with Rubella specific IgM born to Mothers not tested during pregnancy*

| MOTHER | INFANT |
|--------|--------|
| History of rubella (R) or rubella contact (C) and gestation weeks | Birth weight | Sex | Clinical features |
| R/C |  |  |  |
| 12 R | 2860 | M | Hepatomegaly, purpuric rash, anaemia. |
| 6 R | 1644 | F | Deafness, multiple eye defects, patent ductus arteriosus, aortic stenosis, purpuric rash, wide fontanelle, growth retardation (post natal). |
| 8 C* | 2380 | M | Hyposadias, bifid scrotum, Klinefelter's syndrome. |
| 8 R | 3410 | M | Deafness, jaundice, rash, microcephaly, spastic quadriplegia, osteitis. |
| NR NR | 2070 | F | Hepatomegaly, thrombocytopenic purpura. |
| — — | 2920 | M | Systolic murmur, purpura, thrombocytopenia, croup. |
| 6 R | 2235 | F | Post natal growth retardation. |
| 12 R | 2510 | F | Deafness, systolic murmur. |
| NR NR | 2722 | F | Deafness, cataract, and microphthalmia, delayed development. |

NR = not recorded.
* = human immunoglobulin given.
— = no known contact.

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### TABLE 4

*Number and Prevalence Rate per 100,000 Livebirths of Infants with Congenital Rubella in Northern Ireland*

| Year | Number of Livebirths | Number of Congenital Rubella Infants | Rate per 100,000 Livebirths |
|------|----------------------|--------------------------------------|-----------------------------|
| 1977 | 25,437               | 1                                    | 3.9                         |
| 1978 | 26,237               | 5*                                   | 19.1                        |
| 1979 | 28,179               | 11                                   | 39.0                        |
| 1980 | 28,568               | 4                                    | 14.0                        |
| 1981 | 27,297               | 0                                    | —                           |

* includes the two patients born 1978 but not included in study because infected before onset of epidemic.
Table 4 shows the prevalence rate per 100,000 livebirths in Northern Ireland from 1977 to 1981. Before the outbreak the rate was 3.9 and reached a peak of 39.0 in 1979; in the post-outbreak period the rate fell to 14.0 in 1980, and so far no case of congenital rubella born in 1981 has been identified.

DISCUSSION

In Northern Ireland, with a population of 1.5 million, all diagnostic virology is carried out by the Regional Virus Laboratory, and the monitoring of birth defects is undertaken by the Northern Ireland Genetics Service. As both these services are responsible for the whole of Northern Ireland, this facilitated the study of the effects of rubella in pregnancy during the outbreak. The outbreak took place against a background of 81 per cent of pregnant women being immune. Epidemic rubella usually appears in late winter and spring, but in the Northern Ireland outbreak the peaks were in June-July in 1978 and in May 1979. The number of cases of congenital rubella was greater in 1979 than in 1978, a finding similar to Scotland, whereas in England and Wales the pattern was reversed, with more cases occurring in 1978 than in 1979.1 2 The pregnant women with proven rubella lived in the more densely populated eastern area with only two occurring in Londonderry in the north-west, the second largest city in Northern Ireland.

The follow-up of 150 pregnant women with laboratory proven rubella revealed that 69 (46 per cent) had had a therapeutic abortion; in England and Wales the figure was 54 per cent.3 If therapeutic abortion had been unavailable, a further 7 or 8 congenital rubella babies might have been born.

Five problems became apparent during the investigation of the rubella outbreak. The first problem related to the extensive news media coverage during the epidemic. The laboratory was swamped with specimens from many pregnant women who did not have rubella or any contact with rubella, yet were anxious, following the inaccurate reports of the risk of having a congenital rubella baby. The second problem concerned the exposure of pregnant women to rubella. During the outbreak it was noted that the commonest history of exposure was with young children suffering from rubella in her own home or elsewhere. However, in the United Kingdom the policy is to immunise girls only between their 10th and 14th birthdays which is ineffective in preventing rubella in younger boys and girls. Rubella vaccine is also strongly recommended for non-pregnant women of child-bearing age who are seronegative but this policy has not been implemented.

The third problem of rubella infection was that some women and their doctors were unaware of the infection. In 1978 and in 1979, only 53 per cent and 42 per cent of the rubella infected pregnant women had a rash. Since rubella embryopathy can occur with sub-clinical rubella infection,4 5 laboratory tests are important in women with a history of contact with rubella but without clinical symptoms. The fourth problem was that previous rubella immunisation was not a guarantee of immunity in a pregnant woman as in one of our patients. Rubella vaccine does not produce 100% immunity in those immunised.6 In addition, some of those immunised may produce only low rubella antibody titres which may disappear later. The Cendehill rubella vaccine induces a lower seroconversion rate,7 lower serum antibody titres and less rubella specific serum and nasopharyngeal IgA than the
RA27/3 rubella vaccine. Re-infections also are more frequent after Cendehill rubella vaccine.\textsuperscript{15}

The fifth problem, despite widespread publicity of the outbreak in both local and national news media, was that some pregnant women in contact with rubella and who also developed a rash, did not have laboratory investigations carried out (Table 3). One mother, after contact with rubella, was given human immunoglobulin which failed to prevent the infection of the fetus with rubella virus. Human immunoglobulin in normal dosage does not prevent rubella infection but may sometimes prevent the development of symptoms.\textsuperscript{16}

In the 81 pregnant women with proven rubella who went to term, only nine (11 per cent) had abnormal babies. However, it is possible that some apparently normal infants at birth may develop "late onset" disease in infancy.\textsuperscript{17} From several prospective studies, the overall percentage of infants with rubella defects following rubella in the first 4 months of pregnancy is 14.4 per cent.\textsuperscript{18} In our study 14 (78 per cent) of the 18 mothers with congenital rubella infants, had a history of clinical rubella during the first four months of pregnancy. A rubella infection which produces clinical symptoms in the mother is more likely to be associated with rubella defects in the baby than rubella infection without symptoms.\textsuperscript{11, 13}

In our study, rubella infection in the mother during the second month of pregnancy resulted in 10 out of 14 (71 per cent) congenital rubella infants. This finding agrees with the increased risk of defects at this gestation found by Dudgeon.\textsuperscript{18}

Seven of the 18 congenital rubella babies had birth weights below 2500g. Intrauterine and extraterine growth retardation is a feature of congenital rubella infection.\textsuperscript{11, 19} Among our rubella babies there was a high prevalence of deafness, skin rashes, hepatosplenomegaly, congenital heart defects and cataracts, whereas, osteitis, pulmonary infections and microcephaly were much less frequent. Two infants had chest infections which may represent rubella interstitial pneumonitis. One baby with Klinefelter's syndrome has hypospadias and a bifid scrotum. Hypospadias was previously described in a rubella baby.\textsuperscript{19}

The fact that 89 per cent of babies born to mothers with proven rubella were apparently normal at birth raises interesting questions. The virulence of the strain of rubella virus in a particular epidemic may influence the number of fetuses infected \textit{in utero} or the HLA antigens of the mother and fetus may determine susceptibility to infection with rubella virus.\textsuperscript{20}

The prevalence of congenital rubella is difficult to determine because of incomplete reporting of documented or suspected cases, and because of the difficulty in diagnosis. A National Congenital Rubella Surveillance Programme for Great Britain, was established in May 1971.\textsuperscript{21} Following a peak of 11.9/100,000 livebirths in 1973, there was a gradual decline to 2.9 in 1977. In 1978 and 1979 the respective prevalence rates were 7.0 and 9.7.\textsuperscript{22} In Northern Ireland, the prevalence rates for 1978, 1979, and 1980, were 19.1, 39.0, and 14.0, respectively, with a pre- and post-epidemic prevalence of 3.9 and 0 in 1977 and 1981. As a result of the 1978 rubella epidemic in Chicago, 31 infants with congenital rubella were identified, giving a prevalence rate of 48.9 between July 1978 and June 1979.\textsuperscript{23} During the same period in Northern Ireland, the prevalence rate was 32.6.
SUMMARY

Prior to the 1978-79 rubella epidemic in Northern Ireland, 81 per cent of pregnant women were immune to rubella. There was more rubella in 1979 than in 1978. During the epidemic 150 women in the first four months of pregnancy had laboratory proven rubella and of these, 70 (47 per cent) had a recorded rash, 69 (46 per cent) had a therapeutic abortion, and of the 81 women remaining, 9 (11 per cent) had babies with congenital rubella.

A total of eighteen congenital rubella infants were identified; nine were born to mothers with proven rubella, and nine to the mothers who had no investigations. In 14 of the 18 (78 per cent) mothers, there was a history of clinical rubella. Ten mothers were infected with rubella in the second month of pregnancy.

One mother, who had received Cendehill rubella vaccine eight years previously, had clinical rubella during pregnancy and delivered a baby with multiple congenital abnormalities. Another mother received human immunoglobulin after rubella contact in pregnancy; her baby had hypospadias, bifid scrotum, and Klinefelter's syndrome.

The prevalence rate (per 100,000 livebirths) of congenital rubella infants in Northern Ireland, was 19.1, 39.0, and 14.0, for the years 1978, 1979, and 1980, compared with 3.9 in 1977. To date no case of congenital rubella has been identified in infants born in 1981.

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