

Rubella infection during pregnancy in the 1985–86 epidemic: Follow-up after seven years

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Abstract. The study covered 310 pregnant women from southern Poland who were exposed to rubella during the 1985–86 epidemic, none of whom had been vaccinated against rubella. Rubella specific antibodies were detected by hemagglutination – inhibition (HI) tests, and IgM antibodies by enzyme immunoassay (ELISA) (Organon Teknika). Clinical symptoms according to anamnesis were recorded. The consequences of serologically confirmed maternal rubella on the course of pregnancy and on fetal outcome were evaluated. IgM antibodies could be examined in only 10 newborns at delivery or in the first days of life. After seven years, follow-up studies of children born to infected mothers were done. The mental development of 14 of these children was evaluated with Terman-Merrill test. Among 310 women examined during pregnancy, rubella infection was confirmed serologically in 46 cases (14.8%). All but 3 of those had clinical symptoms. The course of pregnancy was observed in 36 of the infected mothers. Only 5 women (22.7%) who had the infection in the first trimester of

pregnancy delivered a healthy child. The rate of complications in pregnancy among women infected in the second trimester was lower, and 8 (66.7%) bore healthy children. All the children born to mothers infected in the third trimester were healthy. Eight of the 10 newborns examined at delivery were IgM positive. Of 29 children congenital rubella syndrome (CRS) was confirmed in 5 cases, CRS compatible or CRS possible in 7 and 3 had congenital infection only confirmed serologically (IgM-positive) without defects or symptoms. Seventeen (58.6%) children were found healthy including the 3 who had congenital infection only. The mental development of 14 children at age 7 was assessed; 10 cases (72%) fell within rank II 130–85, and 4 (28%) were of borderline intelligence. The study indicates that congenital rubella is still a serious problem in Poland. Immunization was introduced only in 1988–89, for 13-year-old girls. Women of child-bearing age should be screened for rubella antibodies and those susceptible to rubella infection should be vaccinated.

Key words: Congenital rubella, Pregnant women, Rubella epidemiology, Pregnancy-complications, Rubella prevention

Introduction

The incidence of rubella and congenital rubella syndrome (CRS) decreased rapidly in the United States and several Western European countries a few years after immunization programs were introduced. This has not happened in Poland, where vaccination was introduced in 1988–1989 [1].

During the rubella epidemic in 1985–86 many pregnant women were exposed. The aim of our study was to examine the course of pregnancy in women with serologically confirmed infection, and the consequences of maternal rubella on newborns.

Clinical symptoms of rubella in children born to infected mothers were recorded at birth and after seven years. The mental development of some of these children was evaluated.

Subjects and methods

During the rubella epidemic of 1985–86, 310 pregnant women who had contact with rubella – infected persons or had symptoms suggesting infection were examined. They had been sent by physicians from the outpatient health units at obstetrics hospitals in Cracow and other hospitals from southern Poland. On the first day that serum was taken for examination, clinical symptoms of rubella infection were recorded, from interviews.

Rubella – specific antibodies were checked with hemagglutination-inhibition (HI) tests and IgM antibodies by ELISA (Organon Teknika).

The course of pregnancy of 36 women with serologically confirmed rubella was observed, and the consequences of maternal infection on the newborn were assessed.

The clinical symptoms of 29 newborns born to

infected mothers were studied; IgM antibodies could be examined in only 10 newborns at delivery or in the first days of life.

Seven years later, in 1992–93, 28 children (one child had died in the first month of life) were examined routinely by a physician in their respective health care units.

The mental development of 14 children whose parents consented to the examination was assessed by a psychologist with Terman-Merrill test [2].

Results

Rubella infection was serologically confirmed in 46 pregnant women (14.8%) aged 18–38 years, average age 26 years. Of these, 29 had been infected in the first three months of pregnancy, 15 in the second trimester and 2 in the third. Serum samples were collected from 2 days to 12 weeks after clinical onset. Rash was the only symptom of infection in about 44% of the women; lymphadenopathy and rash were noted in 37% of the infected women; both of these symptoms plus fever appeared in only 5 rubella – infected pregnant women. In 4 cases arthralgia occurred in addition to rash and lymphadenopathy. Three women had rubella without clinical symptoms.

In all but two of the infected women, rubella-specific IgM antibodies were detected. In women whose sera were not tested by ELISA, infection was confirmed by seroconversion in HI test. There was no correlation between clinical severity and IgM antibody titer. Rubella IgM antibodies are usually detected just before the appearance of rash. They reach peak titer about the seventh day and persist for about a month [3]. In our studies the presence of IgM antibodies lasted longer in 5 cases, to 2–3 months.

Out of 46 women with confirmed rubella infection, the course of pregnancy could be observed in 36 women (10 women did not answer the questionnaire). The outcome of pregnancy in 36 women is shown in Table 1. In 3 cases a decision to terminate pregnancy was taken, in 4 others an abortion took place (information on type of abortion not available). Only 5 women (22.7%) infected in the first trimester delivered a healthy child. Among women infected in

the second trimester, 66% born healthy children. Rubella occurring in the third trimester did not cause complications of fetal outcome.

At delivery or in the first few days of life we were able to examine 10 newborns born to infected mothers. Congenital infection was serologically confirmed in 8 of these newborns. The titer of IgM specific antibodies was from 1:100 to 1:800. Two umbilical cord blood samples were seronegative.

Clinical symptoms in children observed at birth and seven years later are illustrated in Tables 2 and 3. Some degree of deafness was the most common defect (in 8 children), eye defects (retinopathy, cataract) occurred in 3 children, and single cases of cardiac malformation (VSD), hydrocephalus and pancreatitis were also found.

In follow-up observations in 1992–93, additional defects were observed: deafness in 4 more children, and mild hearing loss in 2 more. Behavior disorder and mental retardation were found in 4 others. Among these children 59% were found to be normal while 41% had congenital defects or clinical symptoms of rubella infection (Table 4). Multiple defects were observed in 7 children, and single symptoms in 5.

Psychological testing of children born to rubella-infected mothers included interviews with parents, directed talks with the children, and Terman-Merrill tests [2]. Mental development was scored on the Terman-Merrill scale.

Of the 14 children studied, 10 (72%) fell within rank II 130–85. Four children (28%) were of borderline intelligence.

Five of the 14 children were hearing-impaired (using hearing aids). Two of those 5 were at normal levels of mental development and the other 3 were borderline. Only 1 of the 9 children with normal hearing was borderline; 7 had normal levels of mental development and 1 had an above-average I.Q. (Tables 2 and 3).

Qualitative analysis of the tests for children with borderline intelligence indicated disturbances in the higher forms of mental activity, especially in abstraction and generalization, with no ability to cross into states of formal thinking. These children displayed difficulties in grasping cause-and-effect relations,

Table 1. Outcome of pregnancy in rubella-infected women

| Trimester of pregnancy | No. of infected women | No. of infected women observed | Consequences of infection | | Stillbirth | Termination abortion |
|------------------------|-----------------------|--------------------------------|---------------------------|------------|------------|----------------------|
| | | | None | Present | | |
| I | 29 | 22 | 5 (22.7%)* | 9 | 1 | 7 |
| II | 15 | 12 | 8 (66.7%) | 2 | 2 | – |
| III | 2 | 2 | 2 (100%) | – | – | – |
| Total | 46 | 36 | 15 (41.7%) | 11 (30.6%) | 3 (8.3%) | 7 (19.4%) |

* Percentages of observed women within trimester.

Table 2. Consequences of first-trimester rubella infection on fetal outcome: Follow-up of children at age seven

| MOTHER | | | | | | | |
|--------|-------------------|---------------------------------------|--------------------------------------|-----------|--------------------------|---|----------------|
| No. | Clinical symptoms | Serum collection (weeks) ^x | Rubella antibody titer ^{xx} | | Consequences of rubella | | Diagnosis |
| | | | HI | ELISA IgM | Fetal outcome | Children at age 7 (mental development) ^{xxx} | |
| 1 | ++ | 2 | 160 | 200 | VSD, IgM 400 | Deafness (II-98) | CRS confirmed |
| 2 | +++ | 5 | 160 | 100 | Stillbirth | – | – |
| 3 | ++ | 2 | 256 | > 3200 | Apparently normal | Mild hearing loss (II-81) | CRS possible |
| 4 | ++ | 0.3 | 0 | | Dystrophy, IgM 200 | Deafness (II-71) | CRS confirmed |
| | | 2 | 256 | nt | | | |
| 5 | +++ | 12 | 256 | 100 | Retinopathy | Behavior disorders (II-82) | CRS compatible |
| 6 | +++ | 2 | 160 | > 3200 | Apparently normal | Clinically healthy (II-104) | |
| 7 | + | 2 | 640 | > 3200 | Dystrophy, IgM 400 | Deafness (II-87) | CRS confirmed |
| 8 | +++ | 8 | 80 | 200 | Apparently normal | Clinically healthy (II-89) | |
| 9 | + | 1 | 160 | > 3200 | Apparently normal | Clinically healthy (II-112) | |
| 10 | ++a | 2 | 160 | > 3200 | Cataract, deafness | Mental retardation, deafness | CRS compatible |
| 11 | + | 8 | 256 | 100 | Apparently normal* | Clinically healthy (II-91; II-98) | |
| 12 | ns | 4.5 ^c | 80 | 100 | Apparently normal, IgM 0 | Clinically healthy | |
| 13 | + | 8 | 80 | 100 | Cataract | Mild hearing loss (II-76) | CRS compatible |
| 14 | + | 2 | 256 | > 3200 | Pancreatitis, death | – | CRS possible |
| 15 | ns | ? | 80 | 100 | Hydrocephalus, IgM 100 | Mental retardation | CRS confirmed |

VSD = ventricular septal defect; ^x = after symptom onset; ^{xx} = reciprocal dilution; ^{xxx} = acc. Terman-Merrill test; + = rash; ++ = rash and lymphadenopathy; +++ = rash, lymphadenopathy and fever; a = arthralgia; ^c after contact with infected person; * twins; ns = no clinical symptoms; nt = not tested; ? = data not available.

which produced many errors in inductive and deductive reasoning.

The mental development of the examined children did not differ from that of the normal population.

The results fell into the congenital rubella syndrome (CRS) classification [3] as follows: CRS confirmed in 5 children, CRS compatible in 3, CRS possible in 4, and congenital rubella infection without symptoms in 3 children.

Discussion

During the rubella epidemic in 1985–86 we found rubella infection in 46 pregnant women, as confirmed by the presence of rubella – specific IgM antibodies or seroconversion. All but 3 women also had clinical symptoms. Almost 50% of the women had a high IgM titer (1:1600 – > 1:3200). The low IgM titer (1:100) found in 9 women might have resulted from the rather long period between symptom onset and serum examination (5–12 weeks). Low titer might also have occurred upon reinfection [4]; we could not distinguish between primary infection or reinfection. Three women with low IgM titer bore children with congenital defects or clinical symptoms of infection. The women with confirmed rubella had not been vaccinated before and had not displayed infection earlier in life.

Infection of pregnant women and congenital rubella cases has resulted from the lack of prophylaxis against rubella in Poland. Following the introduction of vaccine in the United States, the incidence of rubella decreased by about 70%, and reported CRS decreased from 2.7/100,000 live births in 1969 to 0.9/100,000 in 1977 [5]. The risk of infection for susceptible women depends on the prevalence of rubella, particularly among children. In the USA, infant and preschool children were vaccinated, while in the United Kingdom pre-adolescent females were [5].

Epidemiological studies in Poland have shown that a high percentage (94–97%) of reproductive-age women have rubella virus antibodies [6]. Children have early contact with the virus. In the 10–11 month age group, 37.3% of the infants had antibodies [6]. Screening for rubella virus antibodies among 22-year-old female students from medical schools in Cracow, which we initiated a few years ago, has shown a higher percentage (10–25%) of seronegative women [7]. The majority of these have been vaccinated, and high vaccination efficiency has been achieved.

Morbidity for rubella in Poland is high: 74,705 cases (200.8/100,000) were reported in 1985 [8] and 462,593 cases (1235/100,000) in the 1986 epidemic year [9]. Data on congenital rubella cases in our country were not published.

Table 3. Consequences of maternal rubella on fetal outcome: Follow-up children at age seven

| MOTHER | | Serum collection (weeks) ^x | Rubella antibody titer ^{xx} | | Consequences of rubella | | Diagnosis |
|--------------------------|---------------------|---------------------------------------|--------------------------------------|-----------|---|---|-----------------------------------|
| No. | Clinical symptoms | | HI | ELISA IgM | Fetal outcome | Children at age 7 (mental development) ^{xxx} | |
| <i>2nd trimester</i> | | | | | | | |
| 16 | ++ | 4 | 128 | 200 | Apparently normal | Clinically healthy | |
| 17 | + | 3.5 | 128 | 1600 | Apparently normal, IgM 100 | Clinically healthy | Congenital rubella infection only |
| 18 | + | 3 | 520 | > 3200 | Apparently normal | Deafness | CRS possible |
| 19 | + | 0.1 | 0 | | Apparently normal | Clinically healthy | |
| | | 2 | 80 | > 3200 | | | |
| 20 | ++ | 3 | 160 | 1600 | Deafness | Deafness | CRS possible |
| 21 | + | 2 | 80 | > 3200 | Apparently normal, IgM 0 | Clinically healthy | |
| 22 | + | 0.6 | 0 | | Apparently normal, IgM 200 | Clinically healthy (II-114) | Congenital rubella infection only |
| | | 3 | 320 | > 3200 | | | |
| 23 | ++ | 0.8 | 320 | > 3200 | Apparently normal | Clinically healthy (II-94) | |
| 24 | + | 6 | 80 | 100 | Apparently normal | Clinically healthy | |
| 25 | ++ | 3 | 256 | 1600 | Stillbirth | | |
| 26 | + | 2 | 32 | 100 | Stillbirth | | |
| 27 | ns | ? | nt | 400 | Apparently normal | Clinically healthy | |
| <i>3rd trimester</i> | | | | | | | |
| 28 | ++ | 0.1 | 0 | | Apparently normal* | Clinically healthy | |
| | | 2 | 256 | nt | | | |
| 29 | + | 12 | 160 | 800 | Apparently normal, IgM 800 | Clinically healthy (II-128) | Congenital rubella infection only |
| <i>Trimester unknown</i> | | | | | | | |
| 30 | Mother not examined | | | | Dystrophy, IgM 800 hepatosplenomegaly, thrombocytopenia | Behavior disorders | CRS confirmed |

^x = after symptom onset; ^{xx} = reciprocal dilution; ^{xxx} = acc. Terman-Merrill test.

+ = rash; ++ = rash and lymphadenopathy; +++ = rash, lymphadenopathy and fever.

* = twins; ns = no clinical symptoms; nt = not tested; ? = data not available.

Table 4. Clinical status of children born following maternal rubella in pregnancy

| Trimester of maternal infection | No. of children | | Total |
|---------------------------------|-----------------|------------------------|-------|
| | Healthy | With clinical symptoms | |
| I | 6* | 9 | 15 |
| II & III | 11* | 2 | 13 |
| Data not available | - | 1** | 1 |
| Total | 17 (58.6%) | 12 (41%) | 29 |

* One pair of twins.

** One child with clinical symptoms of rubella infection, confirmed serologically (IgM 1:200 at age of 4 days) Mother not examined.

The frequency of congenital rubella during the 1978 British rubella epidemic was described by Miller et al. [10]. The rate of infection in infants whose mothers had rubella during the first trimester of gestation was more than 80%. At 13–14 weeks gestation the rate dropped to 54%, and at the end of the second trimester to 25%. During the third trimester the fetal infection rate rose from 25% to 100%, but rubella rarely causes disability at this stage of infection [10].

The results of our studies are similar. Almost 78% of the women infected in the first trimester had complications in the course of pregnancy, and only 22% delivered a healthy child. Among women infected in the second trimester, 67% bore a healthy child. Children born to mothers infected in the third trimester had no clinical symptoms of infection.

The most common defect we observed in 12 children with CRS was hearing impairment of different intensities (deafness or mild hearing loss). Six

of the 8 children with this defect were born to mothers infected in the first trimester of pregnancy. This finding is in accord with others [10–13].

Though the most serious defects follow primary infection, reinfection in pregnancy might also result in intrauterine infection [14, 15]. This is why all women who have had contact with rubella in pregnancy should be examined.

Some defects and fetal damage due to rubella infection can be identified only later in life [16–19]. Children born with CRS may develop a progressive disease such as glaucoma or deafness [16]. Of course there are severe, late-developing manifestations of CRS such as psychiatric and behavioral disorders, mental retardation, cerebral dysfunction and progressive neurological deterioration [11, 20]. To assess the late consequences of congenital rubella we have been conducting follow-up studies of the infected children.

Seven years later, hearing impairment was confirmed in 6 more children, and behavior disorders or mental retardation in 4. Children examined at age 7 by a psychologist showed mental development comparable to that of healthy children. We believe that detection of rubella infection in pregnancy allowed the physician and parents to take special care of the children, early in life. This might have improved their mental development.

Studies on rubella infection during pregnancy in 1985–86 done in England and Wales have shown that selective rubella vaccination does not eliminate congenital infection [21]. Although a dramatic reduction in the number of congenital rubella cases has occurred in the United Kingdom, there were still 362 infections during pregnancy in 1986–87 [22].

Since 1988 all children in the UK have been vaccinated with combined mumps/measles/rubella (MMR) vaccine to interrupt transmission of the virus [16, 23]. In England and Wales there were only 5 cases of CRS in 1990, and only about 3% of the women of child-bearing age were susceptible to rubella [16].

In Poland, vaccination against rubella was not introduced until six years ago, and then only for 13-year old girls. This measure will decrease the frequency of the disease in the long run but will not bring an immediate change in the epidemiological situation.

According to the World Health Organisation program, elimination of congenital rubella in Europe should be achieved by the year 2000. By 1995, rubella vaccination should cover at least 90% of the target population in all European countries [24].

The infection frequencies in this study make it clear that women of child-bearing age in Poland need a comprehensive program of prophylaxis. A broad preventive program against rubella among women was initiated earlier in Israel [25]. Such a program should be based on screening for rubella virus anti-

bodies before pregnancy. All seronegative women and women with low HI antibody titer (< 1:20) should be protected by vaccination.

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