RUBELLA OUTBREAK IN THAILAND 1983-1984 : A STUDY AT SIRIRAJ HOSPITAL

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INTRODUCTION

The clinical manifestations of rubella virus infection usually present as a self-limited, benign disease, characterized by an erythematous maculopapular rash, low grade fever, suboccipital lymphadenopathy and mild upper respiratory symptoms. In children and adults, rubella may be subclinically or may elicit a mild disease with rare complications, but the infection in pregnant women can cause miscarriage, stillbirth or multiple congenital defects (Cooper *et al.*, 1969; Thongcharoen, 1979).

Rubella outbreaks in Thailand occurred in 1967, 1974, and 1978 (Thongcharoen *et al.*, 1969; Chatiyanond, 1979; Thongcharoen *et al.*, 1980).

A study of the recent outbreak of rubella which occurred in Thailand from September 1983 to August 1984, and the results of the clinical and serological investigations in pregnant women are reported herein.

MATERIALS AND METHODS

Subjects : From January 1983 to August 1984, a total of 2,876 pregnant women who visited the hospitals and private clinics in and outside Bangkok were studied. From the presentation 841 were cases suspected of clinical rubella, 1,484 women had history of rubella contact, and 551 remaining cases did not provide any information. The history and physical examinations were recorded in the provided form.

Sera: Approximately five ml of venous blood were taken for serological study. Serum was separated and kept at –20°C until tested. In the cases suspected of clinical rubella, the first blood sample was drawn on the first visit, and the second collected one week later. Usually, paired sera were tested simultaneously except the one taken late after illness, thus only convalescent blood was investigated.

In the contact cases, the first blood specimens were collected on their first visit. Their rubella immunity was assessed promptly for the second blood collection at appropriate time. In non-immune women (HAI antibody titer < 10), the second blood would be obtained at four weeks after contact with the index cases. Time was allowed to cover the incubation period and for increase in the antibody level. If the HAI antibody titer in the first blood was equal to or higher than 10, the second blood would be taken at one week apart. The first sera were retested in parallel with the second sera.

Serodiagnosis for rubella infection was by the demonstration of a four-fold rising of HAI antibody titer in paired sera, or the presence of rubella specific IgM detected by the solid phase immunosorbent hemadsorption test (SPIHAd). Sera with high HAI antibody titer ($\geq$80) but without seroconversion would be subjected to SPIHAd test.

The rubella hemagglutination-inhibition test (HAI) was performed as described (Herrmann, 1979; Louisirirotchanakul *et al.*, 1980). Briefly, serum non-specific inhibitor

was treated with heparin and manganous chloride, the non-specific agglutinator was removed by adsorption with 50% pigeon red blood cells, and then, the heat labile component was eliminated by inactivation at 56°C for 30 min. HEPES saline albumin gelatin buffer pH 6.2, rubella hemagglutinating antigen (Flow Laboratories Inc., USA), and 0.25% pigeon red cells were used in the test.

The technique of solid phase immunosorbent hemadsorption test was modified after Krech and Wilhelm (1979) and Goldwater (1981). Each well of the polystyrene microtiter plate (Nunc Immuno Plate II, U-shape, Denmark) was coated with 50 µl of rabbit anti-human IgM specific for µ-chains (Dakopatts, Denmark) diluted at 1 : 200 in carbonate buffer 0.05 Mp H 9.6. The plate was incubated at 37°C for 1-2 hours and kept overnight at 4°C. Then, the plate was washed 3 times with 0.1% Tween 20 in phosphate buffer saline (PBS-Tween) and the treated serum (as in HAI test) was diluted in HEPES saline albumin (HSA) buffer pH 6.2 starting from the dilution of 1 : 10 to 1 : 1280, the well at the dilution of 1 : 10 was kept as the serum control well. After incubating at 37°C for 2 hours the plate was washed and added with 25 µl of rubella HA antigen at the concentration of 2 hemagglutination units. After overnight incubation, the plate was added with 50 µl of 0.25% pigeon red blood cells, further incubated at 4°C for 2-3 hours and then spun at 700 × g for 1 minute at 4°C. In the specific IgM positive well, thin film of complexes of rubella and red blood cells was still sustained after centrifugation by binding forces between rubella antigen and specific IgM. The complex of the antigen and red blood cells in the negative well was spun down by centrifugal force and appeared as wrinkle button of red blood cells.

The sera positive for the rubella specific IgM were further confirmed by the anti-IgM blocking test. Briefly, the positive, treated serum was diluted in duplicate in vertical rows of the coated plate starting from the dilution of 1 : 5 to 1 : 640 in the volume of 25 µl, then each 25 µl of HSA or anti-human IgM at the dilution of 1 : 100 was added in every well of each row, and further incubated at 37°C for 2 hours. The following steps were as mentioned. The row added with HSA retained high titer of rubella specific IgM, while the one with anti-human IgM would show blocking on activity of the specific IgM and lead to the reduction in the antibody titer.

RESULTS

Rubella infection was not frequently seen or reported in the previous years. The number of the cases became noticeable in September 1983, markedly increased chronographically to its peak in March 1984, and then declined.

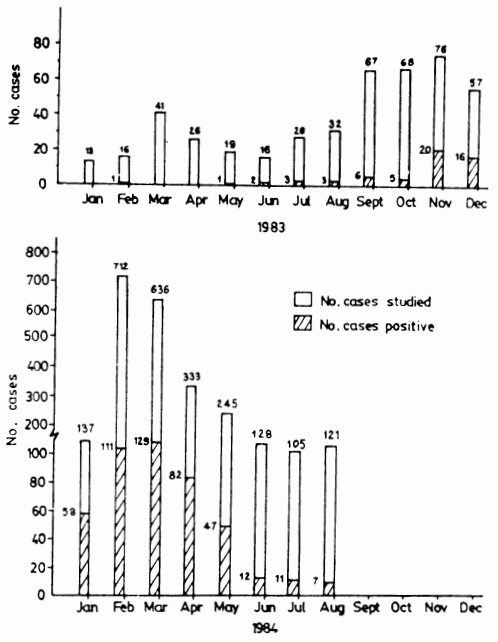

Fig. 1—Monthly distribution of pregnant women requested for rubella serodiagnosis in relation to the positive numbers.

During the rubella outbreak (September 1983-August 1984), the group of 2,685 pregnant women studied consisted of 785 clinical suspected cases, 1,407 contact cases, and 493 cases whose history of infection was not provided. Monthly distribution of the infection in relation to the number of pregnant women requested for laboratory diagnosis during 1983 to 1984 is shown in Fig. 1.

Of 785 clinical rubella suspected, and 1,407 contact cases, the serodiagnosis was inconclusive in 201 and 336 cases respectively thus were excluded from the data analysis. Monthly distribution of rubella cases between September 1983 and August 1984 is shown in Table 1.

At the beginning of the outbreak, only 25% of the cases diagnosed as clinical rubella were proven by HAI or SPIHAd, compared to 75-87% during the middle period of the epidemic. Among 1,071 contact cases, 55 pregnant women developed subclinical infection.

During January to May 1984, 211 cases suspected of clinical rubella and with details of signs and symptoms were analysed for serologic and clinical correlation. It was shown that 173 cases (81.99%) were laboratory proved rubella infection and 38 cases (18%) were not. Among several clinical manifestations observed, only 40% of the rubella cases had lymphadenopathy which was 3 times higher than those of the non-rubella ones. The symptoms of sore throat, coryza-like and photophobia were approximately 2-3 times higher in the patients with rubella. The difference in other symptoms was not remarkable (Table 2).

Table 1

Monthly distribution of rubella cases during the outbreak.

	Clinical suspected cases				Contact cases			
	No. analysed	No. positive (%) as determined by			No. analysed	No. positive (%) as determined by		
		Total	HI	SPIHAd		Total	HI	SPIHAd
Sept 83	16	4 (25.0)	3	1	10	0	0	0
Oct	22	5 (22.7)	4	1	17	0	0	0
Nov	34	17 (50.0)	13	4	24	2 (8.3)	2	0
Dec	22	15 (68.2)	15	0	17	1 (5.9)	1	0
Jan 84	62	53 (85.5)	48	5	43	4 (9.3)	4	0
Feb	103	90 (87.4)	72	18	275	19 (6.9)	6	13
Mar	134	100 (74.6)	68	32	376	6 (1.6)	1	5
Apr	92	70 (76.1)	55	15	127	8 (6.3)	2	6
May	47	32 (68.1)	20	12	99	12 (12.1)	3	9
Jun	17	8 (47.1)	8	0	33	2 (6.1)	0	2
Jul	17	9 (52.9)	8	1	25	1 (4.0)	0	1
Aug	18	6 (33.3)	5	1	25	0	0	0
Total	584	409 (70.0)	319	90	1071	55 (5.1)	19	36

Table 2

Serologic and clinical correlation in rubella and non-rubella proven cases during Jan - May 1984.

Clinical manifestations	Serodiagnosis proved	
	Rubella No. = 173	Non-rubella No. = 38
Rash :		
Generalized	135 (78.0)*	27 (71.0)*
Localized	38 (21.9)	11 (28.9)
Itching	113 (65.3)	23 (60.5)
Fever	149 (86.1)	28 (73.7)
Coryza-like	113 (65.3)	15 (39.5)
Sore throat	119 (66.5)	12 (31.6)
Photophobia	55 (31.8)	5 (13.2)
Lymph node enlargement	70 (40.5)	5 (13.2)
Arthralgia	89 (51.4)	17 (44.7)

* Percentage shown in parenthesis.

Among 435 pregnant women with history of contact with the clinical suspected cases, 19 (4.37%) contracted the infection without apparent disease. The infection seemed to occur by chance and was unlikely to depend on the degree of close relationship between the index and the contact cases. The relationship between the index cases and the contracted cases is shown in Table 3.

Table 3

Index cases and pregnant women who contracted rubella infection.

Index cases	No. contact	No. contracted (%)
Children	66	4 (6.0)
Husband	26	1 (3.9)
Household personnel	102	6 (5.9)
Others: Student, friends, patients	241	8 (3.3)
Total	435	19 (4.4)

DISCUSSION

In Thailand rubella outbreaks have not been reported before 1967. The first outbreak occurred during September 1967 to April 1968 with its peak in February (Thongcharoen *et al.*, 1969) ; and the outbreak which occurred during September 1978 to May 1979 had its peak in March (Thongcharoen *et al.*, 1980). The present study showed the recent outbreak took place during September 1983 to August 1984; and again the peak of the infection was in March. The same observation was reported by the Division of Epidemiology, Ministry of Public Health. The seasonal pattern of rubella epidemics are quite similar. The outbreaks usually began in the rainy season, went on throughout cooler months and reached its peak at the beginning of summer. The incidence of rubella infection seems to follow the same pattern as respiratory diseases. In Western countries, the cases increased during the winter months to a peak

during spring and subsided in summer (Meyer and Parkman, 1982-1983). Increment in transmission rate during the cold months may be due to over crowd of people in closed spaces. The subsidence of the outbreak in summer coincides with the long holidays for school children who were the main target-group for virus attacks (The National Virus Research Institue, 1984), thus, the spread of the disease was cut down.

In our study, HAI and/or SPIHAd were used for rubella serodiagnosis. HAI Ab reached its peak rapidly. Paired sera of which acute blood was drawn later than 7 days after rash did not show seroconversion but expressed high antibody titer, therefore, SPIHAd for the specific IgM determination was needed. Our preliminary study has shown that the specific IgM titer determined by SPIHAd in each case infected recently ranged from 160 to $\geq$ 20480. However, Siriraj laboratory reports the result as "negative" or positive rubella specific IgM in order to simplify the laboratory interpretation. SPIHAd is valid for serum taken not later than 4-5 weeks after rash or 8-9 weeks after day of contact, otherwise, the result comes out as "inconclusive finding".

Upon clinical observations, generalized maculopapular eruption occurred in 78% of the rubella cases, the remaining developed local rash on face, trunk or extremities. Correlation between the clinical and laboratory findings, showed that lymphadenopathy was 3 times more frequent in the rubella than the non-rubella cases but only 40% of the clinically apparent cases developed this symptom. Thus, the clinical diagnosis without laboratory confirmation might be inaccurate, except during the critical period of the epidemic when 80% of the cases with maculopapular rash had rubella infection.

In subclinical infection only 5.14% of the contact cases contracted rubella. The risk to contract the infection seemed to occur by chance, and did not depend on the degree of relationship between the index and the contact cases.

The recent rubella outbreak covered a large area of Thailand. Siriraj Laboratory had investigated many cases referred from several provinces in the north, northeast, east and south of Thailand where laboratory facilities for rubella diagnosis are not available. The diagnosis relying on clinical findings is grossly inaccurate (Hermann, 1983), especially when therapeutic abortion has to come into consideration. So, to expand the laboratory service for rubella is an approach to control the infection. Rubella is a preventable disease, by vaccination; the success of rubella immunization programme in the United States has led to the decrease in congenital rubella cases (U.S. Department of Health and Human services, Public Health Service, 1984). Rubella vaccination has not been included as yet in the Expanded Programme for Immunization of the Ministry of Health of Thailand due to the financial constraints.

For epidemiological background, the fate of the infected pregnant women and their children is now being studied. The rate and the gestational age for termination of pregnancy has to be assessed. Further investigations in the outcome of congenital rubella infection, congenital rubella syndrome, and follow-up of the infected children for late disease manifestations should be carried out by co-operation from health multicenters.

SUMMARY

The recent rubella epidemic in Thailand prevailed from September 1983 to August 1984 with its peak in March. Throughout the outbreak, approximately 70% of the cases diagnosed clinical rubella were laboratory proved. In the middle of the outbreak, accuracy of the clinical diagnosis was 75-87%, while it was 25-33% at the begining and the end. Concerning the clinical findings in rubella, maculopapular rash may be generalized or localized, and lymphadenopathy occurred only in 40% of the clinical cases. Lymphadenopathy and respiratory symptoms appeared 3 times more frequent than those in the non-rubella cases.

Rubella inapparent infection occurred in 5.14% of the contact cases. Acquisition of the disease after contact did not depend on the degree of close relationship between the index cases and the contact cases. Outcome of pregnancy and congenital rubella infection after the outbreak have to be further investigated.

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