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Postpartum Rubella Immunization: Association with Development of Prolonged Arthritis, Neurological Sequelae, and Chronic Rubella Viremia

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Six women developed chronic long-term arthropathy after postpartum immunization against rubella. All individuals developed acute polyarticular arthritis within 12 days to three weeks postimmunization and have had continuing chronic or recurrent arthralgia or arthritis for two to seven years after vaccination. Acute neurological manifestations, consisting of carpal tunnel syndrome or multiple paresthesiae, developed postvaccination in three women. Two have developed continuing active or chronic recurrent episodes of blurred vision, paresthesiae, and painful limb syndromes together with recurrent joint symptoms. Chronic rubella viremia has been detected in peripheral blood mononuclear cell (MNC) populations in five of the six women up to six years after vaccination. In addition rubella virus was isolated from breast milk MNCs in one individual at nine months postvaccination and from peripheral blood MNCs in two of four breast-fed infants studied at 12–18 months of age. Immune responses to rubella virus studied at sequential intervals after vaccination correlated with development of rheumatologic and neurological manifestations.

Rubella immunization of susceptible women in the postpartum period has become part of established medical practice over the last decade. However, several recent findings have raised concern over potential adverse reactions associated with postpartum immunization against rubella, both in the mother receiving the vaccine and in the breast-fed neonate. These concerns have included the development of acute arthritis in 3.7%–18.2% of rubella virus-seronegative women receiving rubella vaccine in the postpartum period [1–7], the detection of rubella virus in the breast milk of 68% of postpartum women receiving either the RA 27/3 or HPV-77 DE/5 rubella vaccine [8, 9], the recovery of rubella virus from >56% of breast-fed infants after postpartum maternal immunization [8, 9], and the recognition that infants exposed in this manner to rubella virus in breast milk have developed transient or no detectable immune responses to rubella virus [9].

The present study further documents the development of chronic recurrent arthritis in six adult women after postpartum immunization against rubella and examines both maternal and infant immune responses to rubella virus in association with persistence of rubella virus in populations of peripheral blood mononuclear cells (MNCs).

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Subjects and Methods

Study population. Six adult women were referred for evaluation to the Immunology Unit of Children's Hospital (Vancouver, British Columbia, Canada) between August 1977 and July 1982 after a history of postpartum immunization against rubella associated with development of chronic recurrent arthritis or arthralgia. None of these cases has been reported previously, with the exception of isolation studies for rubella virus in subject no. 4 [10]. No information was available on the total number of postpartum women receiving rubella vaccine during the study period. Blood samples were obtained at the time of initial assessment and at subsequent follow-up visits and were either processed immediately (for lymphocyte stimulation and viral isolation studies) or stored as serum at −70 C until use.

Rubella serology. HAI studies of rubella virus were performed by using previously described techniques [11]. ELISA tests for rubella virus were performed by using a modification of the technique of

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Vejtorp [12]. Rubella virus antigen was prepared as previously described [13] with the M-33 strain of rubella virus (ATCC VR-315; Dr. Michel Trudel, Institut Armand Frappier, Montreal). Serial twofold dilutions of serum samples were tested in triplicate, and OD readings were compared with standard curves obtained with reference-positive and -negative sera of known concentrations of IgG antibody to rubella virus (calibrated with reference serum from Statens Seruminstitut, Copenhagen). Results are expressed in IU of antibody to rubella virus/ml.

Lymphocyte stimulation by rubella virus. Lymphocyte stimulation assays were performed as previously reported [11]. In brief, lymphocyte populations obtained by sedimentation on Ficoll-Hypaque® (Pharmacia Fine Chemicals, Piscataway, NJ) of blood treated with heparin (10 U/ml) were resuspended in RPMI 1640 medium supplemented with 10% pretested human type AB serum. Serial doubling dilutions of rubella virus HA and HA control antigens (Flow Laboratories, Rockville, Md) were used, and cultures were maintained at 37 C in an atmosphere of 95% air and 5% CO_2 for seven days. Cultures were then pulsed with [^{3}H]thymidine, and stimulation index (SI) values were calculated as the ratio of peak cpm in rubella virus HA antigen–stimulated cultures (mean of triplicate determinations) to the cpm in the corresponding dilution of control antigen–stimulated cultures.

Isolation and characterization of rubella virus. Isolation studies for rubella virus were performed on peripheral blood MNCs as previously described [14]. In brief, MNCs were separated on Ficoll-Hypaque gradients, cultured with phytohemagglutinin for 48 hr, and cocultivated with subconfluent monolayers of rabbit kidney (RK13) cells. Cultures were examined daily for the appearance of CPE, and at weekly intervals the cultures were split 1:2 by treatment with trypsin for up to three passages. Tissue culture supernatants were harvested either on the appearance of gross cytopathology or after the third passage of cultures in which CPE did not develop; the supernatants were stored at −70 C for subsequent detection of rubella virus. Rubella virus plaque assays were conducted in RK13 cells on tissue culture supernatants in the absence or presence of antiserum to rubella virus as previously outlined [14]. Infection with rubella virus in the RK13 cell line produces characteristic microfoci, the development of which is inhibited by specific antiserum in a standard plaque-reduction assay. Further characterization of the isolates was undertaken by interference with echovirus type 11 in primary African green monkey kidney cells as described by Parkman et al. [15]. In addition, polypeptide characterization of the viral isolates was performed as described previously [14] by using the discontinuous SDS-PAGE system described by Laemmli [16].

Results

Table 1 summarizes the joint and neurological reactions observed in six adult women who developed chronic rubella-associated arthritis after postpartum

Table 1. Development of adverse joint and neurological reactions in six adult women after postpartum immunization against rubella.

Patient	Vaccine strain	Time (weeks) of onset postvaccination	Acute reactions		Chronic reactions		Duration of follow-up
			Joint	Neurological	Joint	Neurological	
1	HPV-77 DE/5	2	Polyarthritis	Carpal tunnel syndrome, paresthesiae	Recurrent arthralgia and arthritis	Recurrent carpal tunnel syndrome, paresthesiae, blurred vision	7 years
2	HPV-77 DE/5	2–3	Polyarthritis	. . .	Chronic arthralgia	. . .	6 years 6 months
3	HPV-77 DE/5	3	Polyarthritis	. . .	Recurrent arthritis	. . .	6 years
4	HPV-77 DE/5	2	Polyarthritis	Carpal tunnel syndrome	Rheumatoid arthritis*	. . .	4 years 6 months
5	RA 27/3	3	Polyarthritis	. . .	Recurrent arthralgia	. . .	2 years 9 months
6	RA 27/3	3	Polyarthritis	Paresthesiae	Continuing arthritis and arthralgia	Recurrent paresthesiae, blurred vision	2 years 2 months

* Fulfilling criteria established by the American Rheumatism Association [17].

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immunization against rubella. Subjects ranged in age from 21 to 33 years at the time of immunization, and all had prevaccination titers of HAI antibody to rubella virus of <1:8. None of the subjects had previously received rubella immunization or had a medical history of joint complaints. Four individuals received the HPV-77 DE/5 vaccine, and the remaining two received the RA 27/3 vaccine, at periods ranging from one to 20 weeks postpartum. All pregnancies had been uncomplicated, and five of the six subjects were actively breast-feeding infants at the time of immunization.

Acute joint and neurological reactions postimmunization. All six subjects presented between 12 days and three weeks postimmunization with acute polyarticular arthritis characterized by joint swelling, tenderness or redness, and limitation of movement. The initial episode of joint manifestations lasted between two and six weeks with a gradual resolution of acute symptoms noted. As well, subject no. 1 developed bilateral carpal tunnel syndrome, which was treated with corticosteroid injection and surgical release with no clear effect. She also developed intense pain involving the entire left arm. Subject no. 4 developed bilateral carpal tunnel syndrome, and subject no. 6 developed multiple areas of paresthesiae involving the face and arms.

Chronic joint and neurological manifestations. All six of the subjects under study have developed continuing episodes of arthritis and arthralgia over the prolonged follow-up period, ranging from 26 months to seven years. Among these one individual (subject no. 4) fulfills the diagnostic criteria of the American Rheumatism Association [17] established for rheumatoid arthritis, including the development of chronic symmetrical polyarthritis associated with marked warmth and swelling of joints, limitation of motion, presence of rheumatoid factor, and elevated erythrocyte sedimentation rate. Subject no. 1 continues to have recurrent episodes of arthritis and arthralgia lasting four to six weeks at a time at intervals of three to 12 months. During her flare-ups of active joint disease she also experiences transient periods of "blurred" vision, paresthesiae over her neck and scalp, and nonspecific complaints of disorientation and altered sense of position.

Subject nos. 2 and 3 have had continuing active arthralgia involving multiple joints with morning stiffness and recurrent episodes of overt arthritis lasting weeks to months. Both of these individuals have had dramatic clearing of joint symptoms during the course of intercurrent pregnancies, with recurrence of acute arthritis noted one week before or after delivery. Subject no. 5 had recurrent episodes of arthritis over the first 12 months postimmunization with progressive lessening of symptoms noted and now experiences only mild symptoms of arthralgia lasting for two- to three-week periods at intervals of six to 12 months. Subject no. 6 has had almost continuous polyarticular arthralgia involving knees, hips, elbows, wrists, and shoulders, with swelling in her knees on exertion. In addition she has had continuing complaints of intermittent sudden collapse of both legs with transient symptoms of paresthesiae described as a "numbness" or a "feeling of constriction" over her hands and face.

Immunologic studies pre- and postimmunization. Titers of HAI antibody to rubella virus were <1:8 in all six subjects before administration of rubella vaccine (table 2). ELISA studies performed on preimmunization sera from subject nos. 1, 5, and 6 revealed the presence of significantly elevated levels of IgG antibody to rubella virus structural proteins (M-33 strain).

After immunization all six individuals showed seroconversion by the HAI technique for antibody to rubella virus, although subject nos. 5 and 6 showed a delayed time course and lower peak HAI titers of 1:32 and 1:16, respectively. In addition, these two individuals demonstrated a progressive decline in levels of antibody to rubella virus (by ELISA) over the next two or more years to levels similar to or below those detected preimmunization.

Lymphoproliferative responses to rubella virus were positive (SI, ≥3.0) in five of the six individuals studied postimmunization; the exception, subject no. 4, has remained negative on repeated evaluation. Subject nos. 1, 3, and 6 have undergone a progressive decline in lymphoproliferative responses to rubella virus to negative levels, whereas subject nos. 2 and 5 have remained at positive levels.

Isolation studies for rubella virus. Rubella virus was isolated from peripheral blood MNCs of five of the six mothers at times ranging from nine months to six years postimmunization. Characterization of rubella virus isolates was performed by plaque reduction in the presence of antiserum to rubella virus, interference with echovirus type 11, and viral polypeptide analysis (table 2). Although virus-like cytopathology was detected in RK13 cells cocultured with peripheral blood MNCs from subject no. 2, infec-

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Table 2. Immunologic and virological studies in six women who developed chronic arthropathy after postpartum immunization against rubella.

Patient, timing	Rubella serology		Rubella lymphocyte stimulation			Virus isolation from peripheral blood MNCs
	HAI	ELISA (IU/ml)*	Rubella antigen (cpm)	Rubella control (cpm)	SI†	
1						
Prevaccination	<1:8	6.3	ND	ND	ND	ND
Postvaccination						
7 months	1:64	48	1,867	205	9.1	ND
4 years	1:128	127	1,118	335	3.3	ND
7 years	1:128	116	591	426	1.4	Positive
2						
Prevaccination	<1:8	ND	ND	ND	ND	ND
Postvaccination						
5 years	1:64	45	2,568	445	5.8	Negative
6 years 6 months	ND	47	8,361	752	11.1	ND
3						
Prevaccination	<1:8	ND	ND	ND	ND	ND
Postvaccination						
3 years 6 months	1:64	ND	1,742	173	10.1	ND
4 years	1:128	97	1,879	167	11.3	Positive
5 years	1:128	80	551	359	1.5	ND
4						
Prevaccination	<1:8	ND	ND	ND	ND	ND
Postvaccination						
1 year	1:128	97	5,466	2,033	2.7	ND
4 years 6 months	1:64	80	1,034	642	1.6	Positive
5						
Prevaccination	<1:8	9.3	ND	ND	ND	ND
Postvaccination						
1 year 3 months	1:8	19	23,686	7,225	3.3	Positive
2 years	1:16	12	19,975	5,478	3.6	ND
2 years 9 months	1:16	11	4,876	909	5.4	ND
6						
Prevaccination	<1:8	45	ND	ND	ND	ND
Postvaccination						
7 months	1:8	31	5,094	1,640	3.1	Positive‡
1 year 1 month	1:16	38	1,773	1,900	0.9	ND
2 years 2 months	1:16	28	1,181	872	1.4	ND

NOTE. ND = not done.

* The mean ± 2 SD value for the negative control was 1.0 ± 1.1 IU/ml.

† The negative control was <3.0.

‡ Rubella virus was also isolated from breast milk MNCs at nine months postvaccination.

tious virus was not isolated. Rubella virus was also isolated from breast milk of populations of MNCs from subject no. 6 at nine months postimmunization.

Clinical, immunologic, and virological data on children. Table 3 outlines clinical, immunologic, and virological data on six children born to mothers developing prolonged rubella-associated arthritis after postpartum immunization. No child developed clinical evidence of infection with rubella virus, and subject nos. 2-A and 3-A subsequently received HPV-77 DE/5 rubella vaccine at 21 and 12 months of age, respectively, with no adverse reactions noted. Titers of HAI antibody to rubella virus were negative in all four of the remaining children, with ELISA levels negative in three and positive at borderline low levels in one (subject no. 5-A). The latter child also had highly positive lymphoproliferative responses to rubella virus, whereas the remaining nonimmunized children were negative by this technique. The two children receiving rubella vaccine seroconverted by the HAI and ELISA techniques, with lymphoproliferative responses to rubella virus positive in subject no. 2-A (SI, 10.7) and negative in subject no. 3-A (SI, 0.9).

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Table 3. Immunologic and virological studies in six children born to women who developed chronic arthropathy after postpartum immunization against rubella.

Patient	Age at time of Study	Age at time of Maternal vaccine	Breast-fed	Rubella serology HAI	Rubella serology ELISA (IU/ml)*	Rubella lymphocyte stimulation Rubella antigen (cpm)	Rubella lymphocyte stimulation Rubella control (cpm)	Rubella lymphocyte stimulation SI†	Virus isolation from peripheral blood MNCs
1-A	6 years	16 weeks	Yes	<1:8	1.7	603	350	1.7	Negative
2-A	5 years	6 weeks	No	1:64‡	46.8	6,555	613	10.7	Negative
3-A	4 years	1 week	Yes	1:64‡	16.7	419	443	0.9	Negative
4-A	5 years	1 week	Yes	<1:8	1.0	1,283	525	2.4	ND
5-A	18 months	12 weeks	Yes	<1:8	1.5	ND	ND	ND	Positive
	28 months			<1:8	2.5	19,276	254	75.9	Negative
6-A	12 months	20 weeks	Yes	<1:8	1.7	1,054	369	2.9	Positive
	22 months			<1:8	1.0	614	340	1.8	Negative
	30 months			<1:8	0.5	1,014	536	1.9	ND

NOTE. ND = not done.

* The mean ± 2 SD value for the negative control was 1.0 ± 1.1 IU/ml.

† The negative control was <3.0.

‡ Immunized with HPV-77 DE/5 rubella vaccine at 12–21 months of age.

Isolation studies for rubella virus from peripheral blood MNCs were positive for subject no. 5-A at 18 months of age and for subject no. 6-A at 12 months of age. Rubella virus was not isolated subsequently from peripheral blood MNCs of either of these individuals, and the remaining three individuals tested at older ages were also negative.

Discussion

The present report documents the development of chronic recurring arthritis in six adult women after postpartum immunization with HPV-77 DE/5 or RA 27/3 rubella vaccine. None of these individuals had a preimmunization history of rheumatologic or neurological complaints, and all had onset of arthritis within a two- to three-week period after postpartum immunization. The chronic arthropathy is continuing at follow-up intervals ranging from two to seven years postvaccination with joint manifestations ranging from chronic progressive arthritis to mild continuing arthralgia.

Rubella immunization in the postpartum period has been previously associated with the development of acute arthritis after administration of Cendehill [1–4], RA 27/3 [4–6], and HPV-77 DE/5 [3, 5, 7] rubella vaccines. The incidence of acute arthritis has ranged from 3.7% to 18.2% depending on the strain of vaccine used. Cendehill vaccine has been associated with the lowest incidence of arthritis (3.7%–9.1% of postpartum rubella vaccinees). Acute arthritis has been reported in 8.3% of postpartum women receiving the currently used RA 27/3 rubella vaccine [4] with arthritis or arthralgia noted in 10.7%–24.1% [5, 6]. The highest incidence of acute arthritis in this population has been reported after use of HPV-77 DE/5 vaccine, with acute arthritis noted in 18.2% of postpartum vaccinees [3] and arthritis or arthralgia noted in 31.4%–40.9% [5, 7].

The development of chronic or recurrent arthropathy after rubella immunization has been previously reported by Spruance et al. [18], Thompson et al. [19], and others [10, 20]. In addition, there are increasing reports linking infection with wild rubella virus to chronic forms of arthritis [21–24]. The studies of Ogra et al. [21] and more recently Grahame et al. [22, 23] and Chantler et al. [10] have detected rubella virus or rubella virus antigenic determinants in the synovial fluid of patients with juvenile rheumatoid arthritis and other forms of chronic arthritis. Moreover, the individual case reports of Martenis et al. [25] and McCormick et al. [26] as well as the present report have documented a more direct temporal association between acute infection or immunization with rubella virus and the onset of isolated cases of rheumatoid arthritis. However, a direct causal relation has not yet been established between infection with rubella virus and classic forms of rheumatoid arthritis.

Acute neurological manifestations, including carpal tunnel syndrome and transient paresthesiae, were noted in three subjects in the present study group.

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The onset of symptoms coincided closely with the development of joint complaints. Acute neurological reactions after rubella immunization have been reported extensively after immunization with strain HPV-77 DK/12 [27–29] and to a lesser extent after vaccination with the HPV-77 DE/5 and Cendehill strains [27–30]. Reported symptoms have included carpal tunnel syndrome, multiple paresthesiae, "catchers crouch" syndrome, optic neuritis, and painful arm or leg syndrome and have been attributed variably to nerve compression, peripheral neuritis, myelitis, or myeloradiculitis. The continuation of neurological symptoms for prolonged periods of two and seven years in two subjects in the present postpartum immunization group has been of some concern. In both cases neurological symptoms have been recurrent rather than persistent and are closely associated with periods of flare-up of joint symptoms. This development of prolonged neurological symptoms associated with rubella vaccine has been reported previously by Schaffner et al. [31], although most other studies have emphasized the acute transient nature of these manifestations.

Of particular concern in the present study has been the recovery of rubella virus from peripheral blood MNCs in five of the six women who developed chronic recurrent arthritis after postpartum immunization against rubella. Rubella virus was isolated on multiple occasions in positive individuals at intervals ranging from nine months to six years postimmunization. These studies confirm our earlier reports outlining the association between chronic arthritis associated with rubella vaccine and the presence of prolonged rubella viremia [10, 14]. Of further concern has been the detection of prolonged shedding of virus in breast milk MNC populations in one individual studied at nine months postimmunization. Acute shedding of rubella virus in breast milk has been previously reported at one to three days after the onset of rash in infection with wild rubella virus [32] and 12 days postimmunization after administration of HPV-77 DE/5 rubella vaccine [33]. More recently Losonsky et al. [8, 9] have reported the isolation of rubella virus from breast milk in 11 of 16 postpartum women receiving either HPV-77 DE/5 or RA 27/3 rubella vaccine at intervals from 10 to 17 days postimmunization, with prolonged shedding in one individual to 34 days postimmunization. These authors have also reported the successful isolation of rubella virus or viral antigens from the nasopharynx of nine of 16 breast-fed infants in the two- to four-week period after postpartum maternal immunization against rubella. The isolation of rubella virus from peripheral blood MNCs in two infants in the present study at 12 and 18 months of age may indicate that a state of rubella virus persistence has resulted from the early exposure of the neonate to rubella virus or alternatively may be explained by the recurrent exposure of the child to breast milk carrying infectious virus.

The detection of low levels of antibody to rubella virus detected by ELISA but not the HAI technique in three individuals studied before immunization has been reported previously [11] and suggests that these individuals were undergoing secondary infection with rubella virus on administration of the RA 27/3 rubella vaccine. The significance of this pattern of partial immunity before immunization is not yet clear, but recent studies [11, 20] have indicated that it may be associated with an increased risk of adverse joint reactions after subsequent rubella immunization. Lymphoproliferative responses to rubella virus were lowest in individuals with the most severe joint symptoms and highest in those with minimal continuing joint manifestations.

Attempts to identify immunologic sensitization to rubella virus in the children after maternal postpartum immunization have not been successful, apart from one child who has developed a pattern of HAI seronegativity in the presence of low levels of antibody to rubella virus by ELISA and high levels of lymphoproliferative activity to rubella virus. It is interesting to note that this child was also found to have rubella virus in peripheral blood MNCs at 18 months of age. Two of the remaining children have undergone successful rubella immunization with no adverse reactions whatsoever. Further long-term follow-up studies will be required to determine the effect and significance of early neonatal exposure to rubella virus on antibody or cell-mediated immunity to rubella virus and subsequent responses to current programs of rubella vaccination.

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