Rubella infection in pregnancy

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Abstract

It is over 50 years since a syndrome of congenital abnormalities following maternal rubella infection was first recognised. Despite the potentially devastating effects of the congenital rubella syndrome, immunisation rates are not optimal and infections in pregnancy still occur. Four cases of rubella infection occurring in pregnancy are presented. Laboratory diagnosis of primary infection and reinfection is discussed, and the need for full immunisation in childhood, and of women of child-bearing age is reiterated. *Commun Dis Intell* 1999;23:93-96.

Introduction

Rubella remains a common community infection and continues to be a risk to pregnant women who have either not been immunised or who have waning immunity. Four recent cases of rubella infection occurring in pregnancy highlight the potential risk to the developing foetus of both primary infection and reinfection. For each case, the gestation period stated is the time since the last menstrual period.

Case Studies

Case 1

A 30 year old primigravid woman had routine antenatal investigations at 9 weeks gestation (07/01/97), at which time her rubella IgG was <10 IU/mL by ELISA and rubella IgM was negative. During the 11th and 12th week of pregnancy she had contact with a male co-worker who was diagnosed as having rubella. At that time (24/01/97), repeat testing revealed a rubella IgG of 12 IU/mL. The rubella IgM level remained negative. Subsequent testing two weeks later revealed an IgG >130 IU/mL and positive IgM antibodies (confirmed by IgM sucrose density ultracentrifugation, the reference method). One day later she developed fever, a rash lasting two days and arthralgia. She had previously received rubella vaccination when at school. Repeat testing in parallel of all three samples demonstrated levels for the first two samples that fluctuated between 8 and 17 IU/mL. Her antibody levels prior to exposure were low and non-protective rather than absent. In primary rubella infection, antibodies appear as the rash fades.[1] The detection of IgG in high titre one day prior to the onset of rash is evidence of a rapid

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ISSN 0725-3141
Volume 23
Number 4
15 April 1999

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antibody response consistent with rubella reinfection rather than primary infection.[3] A high IgG avidity index also suggested reinfection. The rash however, was a clinical sign that viraemia had occurred. The patient elected to terminate the pregnancy. Testing of the products of conception did not demonstrate rubella infection, either by standard viral culture or by polymerase chain reaction.[2]

Case 2

A 31 year old woman developed a rash at 17 weeks gestation (5/11/96). Although reinfection was suspected because of a history of vaccination, initial antenatal serology (14/10/96) demonstrated a titre of <10 IU/mL, indicating no evidence of previous vaccination or infection. Serum collected at the time of the rash showed detectable IgM and IgG antibodies, the latter in high titre. Repeat testing of the first serum sample revealed a detectable titre of 18 IU/mL. A third serum sample, collected two weeks prior to the onset of her illness, was retrieved from another laboratory. Testing demonstrated similarly low level IgG titres. Serological testing, including avidity studies was consistent with rubella reinfection. The patient was advised that rubella reinfection at 17 weeks gestation posed little, if any, risk to the foetus. A normal term infant was delivered by vacuum extraction. No foetal abnormalities were evident at birth or on review at six weeks of age.

Case 3

At 22 weeks gestation, a 24 year old aboriginal woman presented unwell with fever and rash (20/11/96) to her general practitioner. Vaccination history was unknown. Rubella specific IgG and IgM was detected. Stored serum from unrelated investigations was retrieved and failed to demonstrate rubella antibodies on the 20/08/96. Documentation of IgG seroconversion confirmed a diagnosis of primary rubella infection. The pregnancy continued to term and a normal foetus was delivered spontaneously. Fortunately, infection at this stage of gestation poses very little risk to the foetus. Although no laboratory investigations or audiometry assessment were performed on the baby, early development has proceeded normally.

Case 4

A 23 year old primigravid woman without a history of rubella vaccination developed a typical rubella illness at 10 weeks gestation. Her mother, a health care worker, did not believe in the benefits of immunisation. A childhood illness characterised by rash was considered by the mother to have been rubella. Serum collected at the time of onset of the rash (13/01/97) contained no demonstrable IgG or IgM rubella antibodies. One week later she seroconverted, with development of elevated IgG and IgM antibody levels. Sucrose density ultracentrifugation confirmed a true IgM elevation. The patient elected to continue with her pregnancy, despite the likelihood of primary infection having occurred at 10 weeks gestation. Subsequently, a male infant was delivered at term. Although there was no evidence of embryopathy clinically at birth, Auditory Brainstem Reaction testing showed responses at 70db but not below and a skeletal survey showed celery stick appearance of the distal femora and proximal tibiae consistent with congenital rubella syndrome. Throat, eye and urine cultures grew rubella virus and the peripheral blood rubella IgG and IgM were positive. On follow up soon after birth, repeat audiology showed minimal hearing loss only.

Methods

In all cases, IgG and IgM antibody assays were performed by a plate ELISA method. IgM detection was by the indirect method. Quantitative results are expressed in international units (IU) with calibration being performed against reference standards of 10, 27, 42, 80 and 130 IU/mL. IgM confirmation was performed by Queensland Health Scientific Services using sucrose density ultracentrifugation, followed by an indirect ELISA assay and expressed as a qualitative result. In all four cases, sources of potential cross-reacting antibodies, such as infection with CMV, EBV, Toxoplasma and Parvovirus were excluded.

Avidity testing was performed for all patients at a later date and was not available at the time of clinical decision making. The IgG ELISA assay had 6.0 M urea added to it. Dissociation of weakly formed antigen–antibody complexes after challenge with a mild protein denaturant (for example, urea) is characteristic of a primary infection whereas rubella reinfection is characterised by highly avid antigen-antibody complexes.[3, 4]

Serological results for rubella antibody testing, including avidity studies are shown in Table 1. The avidity studies confirm the earlier serological diagnoses of rubella reinfection (cases 1 and 2) and primary infection (cases 3 and 4).

Discussion

Two cases of rubella reinfection and 2 cases of rubella primary infection occurring in pregnancy are presented. Distinguishing between the two types of rubella infection can be difficult but is of considerable clinical importance. The risk of foetal abnormality is far greater following primary infection than reinfection, though a number of reports in recent years have demonstrated that reinfection carries a small but definite risk of long term sequelae.

The estimated risks of foetal damage following primary infection is highest when infection occurs in the first 8 weeks after the last menstrual period, when 90 – 100% of foetuses will become infected and up to 100% of the infected foetuses will develop major clinical defects.[5] Such defects typically include those affecting the heart, vision and auditory function. The risk of both foetal infection and the incidence and severity of congenital defects progressively declines after the first trimester and the risk of any defects after 17 weeks gestation is rare, though may account for some cases of deafness observed after rubella infection in pregnancy.[5] It is important to note that some features of congenital rubella syndrome, such as deafness, may not be detected at birth, and so careful follow up is required.

The risk of foetal infection following maternal reinfection has been variably estimated as 0[6, 7] to 30%,[3] though it is generally accepted that less than 5% of foetuses will become infected when maternal reinfection occurs within the first trimester of pregnancy[3, 5] and that a proportion less than this will develop congenital defects. No cases of rubella reinfection infecting the foetus have been reported after 12 weeks gestation.[8] Most reinfections are

Table 1. Patient results: Rubella serology, avidity testing and characterisation of rubella primary infection from reinfection

	Serology measurements (IU/mL, positive or negative)			
Test	Case 1	Case 2	Case 3	Case 4
Initial antenatal serology	IgG <10	IgG <10	IgG <10	IgG <10
Repeat initial serology (tested in parallel)	IgG 17 IgM neg	IgG 18I gM neg	IgG<1 0IgM neg	IgG<10
Testing at time of rash (tested in parallel)	IgG>130IgM pos IgM UC pos	IgG 130 IgM pos IgM UC equiv	IgG >25 IgM pos IgM UC pos	IgG >25 IgM pos IgM UC pos
Follow-up testing	Not done	IgG >130 IgM pos IgM UC pos	Not done	Not done
Avidity studies	High	High	Low	Low
Diagnosis	Reinfection	Reinfection	Primary Infection	Primary Infection

UC = sucrose density ultracentifugation; to separate IgM from IgG in a serum sample

asymptomatic.[8] Maternal rash is a clinical sign of viraemia but is seldom noted in cases of rubella reinfection, though some women report a non-specific illness.[8, 9] When rash does occur with rubella reinfection, as occurred in the first two cases presented, the risk of foetal damage may more closely match that for primary infection at equivalent gestation, though this has never been clearly documented.

The incidence of congenital rubella infection is monitored by the Australian Paediatric Surveillance Unit (APSU). From May 1993 to December 1997, there have been 24 cases of congenital rubella infection reported to the APSU, of which 5 were born without defects.[9] The estimated incidence in Australia of congenital rubella infection with defects is 1.5/100 000 live births. Seven cases born in 1996 were reported.[10] Two cases had a history of maternal vaccination and represent possible rubella reinfection (or vaccine failure). Both infants had congenital defects; one infant died.

When a pregnant patient has contact with a known or suspected rubella case, or has a non-specific viral-like illness with or without rash, clinicians are advised to perform serial rubella antibody tests, regardless of vaccination status. Congenital rubella syndrome has been documented to occur in Australia despite documented pre-pregnancy levels considered to afford good immunity.[11-13]

While some authorities, notably in the United Kingdom, require proven evidence of successful seroconversion following either vaccination or wild type infection to establish a diagnosis of reinfection, this documentation is commonly lacking in everyday practice. Most reinfections occur in subjects previously vaccinated. Evidence of vaccine efficacy is not usually sought until a woman presents with her first pregnancy. The distinction between primary and secondary infection is ultimately in the hands of the serology laboratory. A single IgG antibody measurement of less than 10 IU/mL would be reported as showing no evidence of prior rubella vaccination or infection by most laboratories, including our own (and hence susceptible to primary infection). A value of 10-15 IU/mL would be reported by our laboratory as indicating that antibodies are detectable but at a level not necessarily providing protection from (re)infection. Repeat testing of the same sample may give results variably suggesting that the patient is, or is not, at risk for primary infection yet still be within the range of two standard deviations (SD) of the cut-off of 10 IU/mL. Calculation of distribution parameters for the reference standard of 10 IU/mL revealed a range within 2SD of 7.2-12.8 IU/mL for the ELISA assay. It is important that testing laboratories investigate possible cases of rubella infection in pregnancy by careful, reproducible parallel testing. Laboratories should be aware of the coefficients of variation for their assay.

Serum samples that predate or occur within 7 - 10 days of a presumed rubella exposure can be extremely valuable in determining pre-exposure immune status to enable one to establish whether a significant rise in IgG antibody level subsequently occurs. It may be necessary to pursue a history of unrelated serological testing or previous rubella antibody measurement in order to discover a source of stored serum (as was done for cases 2 and 3). While IgM was detected in our two cases of reinfection, this does not invariably occur.[13] A significant rise in IgG level is required to diagnose rubella reinfection serologically. Unlike primary infection, reinfection is characterised by high avidity antibody binding. Avidity testing was performed by our laboratory but at a later date. It requires careful technique but is a useful adjunct to antibody detection. However, unless the testing laboratory is regularly performing avidity testing, turn around time may not be rapid enough for a clinician and patient contemplating termination of pregnancy.

The schoolgirl rubella vaccination programme commenced in 1970-71. In 1988-89 combined measles, mumps and rubella (MMR) vaccination was recommended for all infants aged 12 months. Australian states and territories introduced vaccination of all teenage boys and girls in the period 1994-96, replacing the schoolgirl vaccination programme. More recently (1998), the age for the second MMR vaccine has been lowered to age 4 - 5 years,

principally to improve immunity against measles in children. While eradication of measles and rubella is now a real possibility, there remains a large pool of rubella susceptible males, typically aged between 10 - 25 years, in the community today. Unfortunately childhood vaccination in this country has reached worryingly low levels. When surveyed in April 1995, only 35% of children aged two years were fully vaccinated, although the rubella vaccination rate was higher (81%).[14] As a greater proportion of the community acquires antibodies through vaccination rather than naturally occurring disease, primary disease will become less common. Infections encountered are more likely to be reinfections, generally seen in those with low post-vaccination antibody titres.

In the past, women were at the greatest risk of exposure through contact with their own children. Now susceptible women are at most risk of becoming infected by contact with infected fellow students or male co-workers. Migrant women may be more likely not to have been vaccinated prior to becoming pregnant.[15]

As it is clear that immunity following vaccination, especially a single dose in adolescence, may decline over time, the importance of checking antibody titres with each and every pregnancy must be stressed. A pregnant woman with no or low immunity needs to be vaccinated immediately after delivery and antibody status checked after 3 months. It is important that vaccination not be given in the three months following administration of immunoglobulin (with the exception of anti-D Rh immunoglobulin) or whole blood transfusion, as there may be some interference with antibody response to the vaccine. Ideally, antibody status could be checked prior to a planned pregnancy so that vaccination could be given, if indicated, prior to conception. This may be especially applicable where first pregnancies are occurring many years after vaccination. It is recommended that women wait 2 months following vaccination with live attenuated rubella virus before conceiving.[16] Where vaccination has inadvertently occurred during pregnancy, no documented cases of foetal abnormality have been recorded.[16] Whenever a pregnant woman has had contact with an illness that might be rubella, clinicians should be encouraged to check immune status and look for evidence of acquired infection. This requires appropriately timed serological investigation; at least 28 days (maximum incubation period plus 7 days) after a rubella contact should be allowed to reliably detect an antibody response. Clinical illness cannot be relied upon to detect most cases of reinfection.

Congenital rubella syndrome remains a preventable disease provided that the current childhood immunisation schedule is successfully implemented and that protective immunity is maintained in women of child-bearing age.

When infection does occur in pregnancy, careful serological investigation can help distinguish between primary infection and reinfection, in order that patients can be best informed of the potential risks to the foetus.

Acknowledgments

We acknowledge the services of Queensland Health Scientific Services for the performance of rubella serology following ultracentrifugation and rubella virus PCR.

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