14 A vs National Blood Authority [2001] 3 *All ER* 289.
15 Sanguis Study Group. Use of blood products for elective surgery in 43 European Hospitals. *Transfusion Med* 1994;4:251-68.
16 Association of Anaesthetists of Great Britain and Ireland. *Blood transfusion and the anaesthetist: red cell transfusion*. London: Association of Anaesthetists of Great Britain and Ireland, 2001.
17 Blajchman MA, Dzik S, Vamvakas EC, Sweeney J, Snyder EL. Clinical and molecular basis of transfusion induced immunomodulation: summary of the proceedings of a state-of-the-art conference. *Transfusion Med Rev* 2001;15:108-35.
18 Prowse CV. Alternatives to standard blood transfusion: availability and promise. *Transfusion Med* 1999;9:287-99.
19 Watson N, Taylor C. Allogeneic blood transfusion—the alternatives. *Hosp Pharmacist* 2000;7:124-9.
20 NHS Executive. *Better blood transfusion*. London: Department of Health, 1998. (Health Service Circular (HSC) 1998/224.)
21 Clark P, Rennie I, Rawlinson S. Effect of a formal education programme on safety of transfusions. *BMJ* 2001;323:1118-20.
22 Council of Europe expert committee in blood transfusion study group on pathogen inactivation of labile blood components. Pathogen inactivation of labile blood products. *Transfusion Med* 2001;11:149-75.
23 Dumont LJ, Luka J, VandenBroeke T, Whitley P, Ambruso DR, Elfath MD. The effect of leukocyte-reduction method on the amount of cytomegalovirus in blood products: a comparison of apheresis and filtration methods. *Blood* 2001;97:3640-7.
24 Roth WK, Weber M, Seifried E. Feasibility and efficacy of routine PCR screening of blood donations for hepatitis C virus, hepatitis B virus and HIV-1 in a blood bank setting. *Lancet* 1999;353:359-63.
25 Koenigbauer UF, Eastlund T, Day JW. Clinical illness due to parvovirus B19 after infusion of solvent/detergent-treated pooled plasma. *Transfusion* 2000;40:1203-6.
26 Pamphilon D. Viral inactivation of fresh frozen plasma. *Br J Haematol* 2000;109:680-93.
27 Barbara J. Pathogen inactivation treatment of platelet components: advancing from theory to clinical practice. *Semin Hematol* 2001;38(4 suppl 11).

Lesson of the week

Interpretation of rubella serology in pregnancy—pitfalls and problems

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Clinical and laboratory expertise is essenrial for evaluating rubella specific IgM test results in pregnancy

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Rubella acquired in the first 12 weeks of pregnancy is associated with a 90% risk of congenital malformations. Although rare in many industrialised countries, because of the success of vaccination programmes, rubella continues to occur where uptake of the vaccine is low and in many developing countries with no vaccination programme. The World Health Organization has therefore encouraged all countries to assess their rubella status and introduce immunisation and surveillance, if appropriate.[1] As the clinical diagnosis of rubella is unreliable, serological tests are needed for a diagnosis, especially when a patient is pregnant or has been in contact with a pregnant woman.[2] Diagnosis is usually made by detection of rubella specific IgM. Although commercial assays are available, they vary in format, sensitivity, and specificity.[3] Furthermore, rubella specific IgM may be present a year or more after natural infection or vaccination and after asymptomatic reinfection.[4–8] False positive results may also be due to cross reacting IgM antibodies or rheumatoid factor.[9] Consequently, in countries with limited laboratory facilities and expertise, diagnosis of rubella in pregnancy is problematic. It is essential that laboratory results be interpreted in the context of full clinical details, to avoid misinterpretation of results and to minimise anxiety for the patient, especially if termination of pregnancy is considered. Here we discuss six cases referred initially to the Department of Virology at Guy's and St Thomas's Hospital Trust from February to September 2000.

Case reports

Clinical information on the patients and laboratory test results are shown in the table. Five patients were referred from outside the United Kingdom, four because rubella specific IgM had been detected in the absence of a rash.

Patients 1 to 4 had no history of rash or contact with a rash, and in patients 2, 3, and 4 rubella IgM tests had been conducted without any clear clinical indication. In all of these patients except patient 3 positive rubella IgM results were confirmed, but rubella IgG avidity was high, indicating past rather than recent infection. In addition, detection of IgG antibodies to the E2 glycoprotein of rubella virus by immunoblot in patients 1 and 2 indicated that primary infection occurred more than five months previously, indicating persistence of rubella IgM.[10] Rubella specific IgM was not detected in serum samples from patient 3 when tested in the United Kingdom. Prenatal diagnosis offered to patients 1, 2, and 3 at 18-22 weeks' gestation provided further reassurance that their babies were unlikely to have congenital rubella infection (table).[11 12]

Rubella IgM antibodies in case 4 were detected locally using indirect enzyme immunoassays, which are more likely to give non-specific results than antibody capture assays.[3] Retesting in two reference laboratories gave negative results in M antibody capture assays but a weak positive result in an indirect assay. This patient was therefore reassured that she had not had primary rubella, as she had a history of rubella vaccination and high avidity rubella specific IgG was detected.

Patient 5 was of particular concern. Rubella specific IgM was not detected locally, but the patient's obstetrician misinterpreted the laboratory results and advised termination of pregnancy.

Patient 6 presented with rash and fever at 33 weeks' gestation. A vesicular scrape was taken and a diagnosis of chickenpox made by immunofluorescence. However, low positive results were obtained in rubella IgM and parvovirus B19 IgM assays. Such false positive IgM results may be explained by cross reacting antibodies known to be induced by some viral infections and autoimmune disease.[6 9 13] It is therefore of interest that this patient gave a weak positive result in the Rose Waaler assay and during childhood had suffered from rheumatic fever and required mitral valve replacement.

Discussion

These cases show that results of rubella IgM assays conducted on serum samples from pregnant women should always be interpreted with caution. Any history of rash

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Clinical details of patients and reference laboratory results

Patient	Details	Gestation (weeks) at referral	Rubella serology			Prenatal diagnosis	Conclusions and outcome
			IgM*	IgG†	Avidity		
1	Flu-like illness, no rash, at 10 weeks' gestation. No known contact. No history of rubella vaccination. Rubella antibodies detected in 1991	21	+/+/+	+	High	Amniotic fluid PCR negative. Fetal blood PCR and rubella IgM negative. Ultrasound normal	• Past and not recent infection • Persistent IgM response • Baby normal‡
2	Upper respiratory tract infection at 6 and at 15 weeks' gestation. No rash or known contact. No history of rubella vaccination or screening	18	–/+/+	+	High	Amniotic fluid PCR negative. Ultrasound normal	• Past and not recent infection • Persistent IgM response • Baby normal with no evidence of congenital rubella infection
3	No rash or known contact. No history of rubella vaccination or screening	9	–	Not done	Not done	Amniotic fluid PCR negative	• False positive IgM in local laboratory • Baby normal with no evidence of congenital rubella infection
4	No rash or known contact. History of rubella vaccination but no history of screening	18	–/–/+	+	High	Not done	• Past and not recent infection • False positive IgM in indirect assays • Baby normal‡
5	Daughter had rash, but no symptoms in patient. Termination of pregnancy recommended. No history of rubella vaccination. Tested positive to rubella antibody on screening in 1995	20	–	+	Not done	Not done	• Local misinterpretation of results • Baby normal‡
6	Vesicular rash	33	+/–	–	High	Not done	• No evidence of primary rubella or reinfection • Non-specific IgM response • Baby normal‡

PCR=nested reverse transcription polymerase chain reaction. *Some serum samples were tested by more than one assay. †In patients 1 and 2, IgG antibodies to the E2 glycoprotein of rubella virus were detected by immunoblot. ‡Serum not obtained from baby.

or contact with rash, previous rubella testing, and history of vaccination should be taken into consideration.[2] Tests for rubella IgM are not indicated unless there is a history of rash in a pregnant woman or contact with a rubella-like rash. Unnecessary tests for rubella IgM may lead to problems in interpretation, because the positive predictive value of rubella IgM results has declined in countries where rubella seldom occurs. These cases show that problems may arise as a result of:

- False positive rubella IgM results
- No access to other assays, such as rubella IgG avidity[14 15]
- Limited experience of rubella diagnosis and its pitfalls (for example, persistent specific IgM)[4 7]
- Misinterpretation of laboratory results.

In our experience results from about 2% of serum samples tested for rubella IgM will be difficult to interpret. In other countries this problem may be more common.[7] To manage these cases close collaboration between obstetricians and virologists is essential at all stages, to avoid errors and unnecessary terminations and to decide whether prenatal diagnosis is indicated.[2–12]

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1 Department of Vaccines and Biologicals, WHO. Report of a meeting on preventing congenital rubella syndrome: immunization strategies, surveillance needs. Geneva: World Health Organization, 2000. www.who.int/vaccines-documents/DocsPDF00/www508.pdf (accessed 14 May 2002).
2 Best JM, Banatvala JE. Rubella. In: AJ Zuckerman, JE Banatvala, JR Pattison, eds. *Principles and practice of clinical virology*. 4th ed. Chichester: John Wiley, 2000:387-418.
3 Hudson P, Morgan-Capner P. Evaluation of fifteen commercial enzyme immunoassays for the detection of rubella-specific IgM. *Clin Diagn Virol* 1996;5:21-6.
4 Banatvala JE, Best JM, O'Shea S, Dudgeon JA. Persistence of rubella antibodies following vaccination: detection of viremia following experimental challenge. *Rev Infect Dis* 1985;7 (suppl 1):S86-90.
5 Best JM, Banatvala JE, Morgan-Capner P, Miller E. Fetal infection after maternal reinfection with rubella: criteria for defining reinfection. *BMJ* 1989;299:1773-5.
6 Thomas HIJ, Barrett E, Hesketh LM, Wynne A, Morgan-Capner P. Simultaneous IgM reactivity by EIA against more than one virus in measles, parvovirus B19 and rubella infection. *J Clin Virol* 1999;14:107-18.
7 Enders G. Qualitätssicherung in der Serodiagnostik bei der Mutterschaftsvorsorge: Qualitätssicherung und aktuelle Aspekte zur Serodiagnostik der Röteln in der Schwangerschaft. Symposium Moderne Aspekte der Mikrobiologischen Diagnostik, Kurzfassungen von Vorträgen des 3. Symposium am 04. Dezember 1996 in Berlin. *Clin Lab* 1997;43:1019-32.
8 Thomas HIJ, Morgan-Capner P, Roberts A, Hesketh L. Persistent rubella-specific IgM reactivity in the absence of recent primary rubella and rubella reinfection. *J Med Virol* 1992;36:188-92.
9 Almeida JD, Griffith AH. Viral infections and rheumatic factor. *Lancet* 1980;ii:1361-2.
10 Pustowoit B, Liebert UG. Predictive value of serological tests in rubella virus infection during pregnancy. *Intervirology* 1998;41:170-7.
11 Enders G. Fetale Infektionen. In: Hansmann M, Feige A, Saling E, eds. Pränatal- und Geburtsmedizin. Berichte vom 5. Kongreß der Gesellschaft für Pränatal- und Geburtsmedizin vom 21. bis 23. Februar 1997. Meckenheim: DCM Druck Center, 1998:76-82.
12 Revello MG, Baldanti R, Sarasini A, Zavattoni M, Torsellini M, Gerna G. Prenatal diagnosis of rubella virus infection by direct detection and semi-quantitation of viral RNA in clinical samples by reverse transcription-PCR. *J Clin Microbiol* 1997;35:708-13.
13 Enders G, Miller E. Varicella and herpes zoster in pregnancy and the newborn. In: Arvin AM, Gershon AA, eds. Varicella zoster virus: basic virology and clinical management. Cambridge and New York: Cambridge University Press, 2000.
14 Thomas HIJ, Morgan-Capner P. Rubella-specific IgG1 avidity: a comparison of methods. *J Virol Methods* 1991;31:219-28.
15 Böttiger B, Panum Jensen I. Maturation of rubella IgG avidity over time after acute rubella infection. *Clin Diagn Virol* 1997;8:105-11.

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