

Guidelines on the management of, and exposure to, rash illness in pregnancy (including consideration of relevant antibody screening programmes in pregnancy)

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Summary: *These guidelines, produced by the Public Health Laboratory Service (PHLS) aim to help decision making in the investigation and management of pregnant women who have 'a rash compatible with a systemic viral illness', or who have contact with a person with such an illness. They address particularly rubella, parvovirus B19, and varicella-zoster virus infection, but consider other infective causes of rash illness in the United Kingdom. The guidelines give the magnitude and degrees of risk to the fetus in terms of outcomes for the gestation at which maternal infection occurs.*

Recent changes in epidemiology and management lead to the following specific advice, which both updates and re-affirms established guidelines.

- *All pregnant women with a non-vesicular rash illness should be investigated simultaneously for rubella and parvovirus B19 infection.*
- *All pregnant women who have had significant contact with a person suffering from a non-vesicular illness should be investigated for asymptomatic parvovirus B19 infection, and for asymptomatic rubella infection unless there is satisfactory evidence of past rubella infection (vaccine or natural infection). A significant contact is defined as being in the same room for over 15 minutes, or face-to-face contact.*
- *Specific investigation to detect asymptomatic rubella reinfection is not advised.*
- *It is essential to confirm by adequate laboratory investigation all cases of possible rubella and parvovirus B19 infection in pregnancy.*
- *Management of proven rubella in pregnancy should be based on established risks of adverse outcome.*
- *Women with proven parvovirus B19 infection in the first 20 weeks of pregnancy should be followed by regular ultrasound scanning, and referred to Regional Units of Fetal Medicine if hydrops fetalis is detected.*
- *Parvovirus B19 antibody screening in pregnancy is not advised, and consensus has been reached on the procedures to be followed for rubella antibody screening, including the concentration of antibody that reflects past infection.*
- *Oral antiviral treatment (aciclovir) is advised with informed consent for pregnant women who present within 24 hours of onset of varicella.*
- *Referral to hospital and intravenous antiviral treatment is indicated for pregnant women with complications and/or risk factors, or whose illness continues for six days or more.*
- *Pregnant women exposed to varicella or herpes zoster can be reassured as to their protection if they themselves have a history of varicella or herpes zoster. If this history is uncertain or not known, susceptibility should be tested, and varicella-zoster immunoglobulin (VZIG) offered to those found susceptible if within 10 days of first exposure.*
- *Infants whose mothers develop varicella 7 days before to 7 days after delivery should be given VZIG, and aciclovir if onset was 4 days before to 2 days after delivery.*

Key words:
 hydrops fetalis
 infection control
 measles
 parvovirus B19
 pregnancy
 rubella
 rubella syndrome,
 congenital
 varicella

Introduction

These guidelines consider the management of the pregnant woman with, or exposed to, rash illness, with a particular focus on rubella, parvovirus B19 and varicella-zoster virus infection. They update and consolidate previous guidance¹⁻⁴, and address aspects for which there was previously no consensus advice. These guidelines use 'a rash compatible with a systemic viral illness' as a definition of a rash illness. They do not include localised skin disease, such as herpes zoster and that caused by herpes simplex virus.

A Joint Working Party of the Advisory Committees of Virology and Vaccines and Immunisation was convened by the Public Health Laboratory Service (PHLS) to prepare these guidelines, based upon evidence where available and consensus where not. Membership (annex A) included epidemiologists, public health specialists (CsCDC), laboratory virologists, general practitioners (GPs), infectious disease specialists, an obstetrician and a midwife.

The guidelines do not attempt to embrace all aspects of management; those areas for which management is well established are only briefly considered, if at all, but relevant sources of further and background information are given. These guidelines aim to help in decision making, but have no legal status. Updating of the guidelines will be required as and when new evidence becomes available, and at least within five years of release.

Background

Although rubella, parvovirus B19, and varicella-zoster virus are the infections that are of most relevance because of their potential impact on the fetus and neonate, pregnant women will present with a generalised rash (or contact with a rash) the cause of which may not be clinically apparent. Therefore, the guidelines embrace management from the first presentation but acknowledge that often, particularly for varicella-zoster, the clinical and/or epidemiological features may be sufficiently suggestive of the aetiology to form the basis of investigation and management.

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Infections which may present with a rash illness in pregnant women in the UK include:

- rubella;
- parvovirus B19;
- varicella-zoster virus;
- measles;
- enterovirus;
- infectious mononucleosis (Epstein-Barr virus or, very rarely, cytomegalovirus);
- syphilis;
- streptococcus;
- meningococcus;
- a range of other infections not endemic within the UK, and that only need consideration if there is a history of recent travel to an endemic area (e.g. dengue).

Syphilis, streptococcal and meningococcal disease and imported infections are not considered further as clinical and epidemiological information would focus appropriate investigation and diagnosis. Table 1 shows the characteristic features and incidence of those infections in the UK of particular significance for the fetus, i.e. rubella, parvovirus B19 and varicella-zoster.

All requests for laboratory investigation should include the following information to enable the results to be reported with the correct interpretation:

- full demographic details;
- gestation of pregnancy (date of last menstrual period);
- date of onset, clinical features, type and distribution of any rash illness;
- past history of rubella and any other antibody testing and/or rubella vaccine administration (plus dates/places);
- any known contacts with individuals suffering from a rash illness, and dates of contact.

Antenatal sera should be retained for at least one year to assist diagnosis in a later pregnancy and investigation of the neonate. This may include exposure to varicella-zoster virus and parvovirus B19, when the availability of such sera for testing can be invaluable in the rapid assessment of susceptibility.

Information for the pregnant woman

Information and advice to pregnant women should reflect the guidelines set out in this document. At booking the midwife should:

- enquire if the woman has previously had chickenpox or shingles, and if not, advise that she make *urgent* contact if she develops chickenpox-type vesicles in pregnancy, or has contact with chickenpox or shingles;
- advise the woman to inform her midwife, GP or obstetrician urgently if she develops a rash in pregnancy;
- advise the woman to inform her midwife, GP or obstetrician if she has 'contact' in pregnancy with someone who has a rash. ('Contact' is defined in the section headed 'The pregnant patient in contact with a rash illness'.)

Women should be provided with unbiased information regarding screening and diagnostic tests, the meaning and consequences of both, what to expect in terms of results and further options for management. They should feel free to exercise whatever options they choose. Prior to screening or diagnostic tests the minimum standards of information provided for women should include:

- The fact that all the tests to establish the initial diagnosis will be on blood samples obtained by phlebotomy. The requirement for more invasive tests, e.g. amniocentesis, is uncommon, and is only required in the rare situations detailed in these guidelines.

On the rare occasion, a test may give inconclusive results and further testing may be necessary, which may prolong the time to obtain the results; on occasions, further sera may be required. If investigation is undertaken some weeks after rash onset or significant contact, it may not be possible to confirm or refute a possible diagnosis.

- How long the test results will take (consult local laboratory).
- Who will supply the test results.
- Who will discuss future management of the pregnancy.
- Who the patient should contact, if they have any unanswered queries or concerns.

Written information should be provided to back-up verbal advice or information given. The use of an interpreter for women who do not speak English and the use of audiotapes to reiterate verbal discussion is good practice. All discussions, advice and care management plans should be documented.

All pregnant women with rash illness, or who have had significant contact with a person with a rash illness, should be referred for medical management.

Specific infections

Rubella

The clinical features and consequences for the fetus of primary rubella in pregnancy are well established⁵. The unreliability of a clinical diagnosis of rubella is accepted⁶. The risk to the fetus of primary rubella in the first 16 weeks of gestation is substantial (table 1), with major and varied congenital abnormalities being associated with infection in the first trimester, and a lesser risk, limited to deafness, in the fourth month⁵. Rubella infection prior to the estimated date of conception or after 20 weeks carries no documented risk^{5,7}, and rubella between 16 and 20 weeks gestation carries a minimal risk of deafness only⁸.

A rubella reinfection is defined as rubella infection in someone who has previously had either documented natural rubella virus infection or successful rubella immunisation⁹. Maternal reinfection is usually subclinical and diagnosed by changes in antibody concentration (IgG and/or IgM) only. The risk to the fetus of subclinical maternal reinfection in the first 16

weeks gestation has not been precisely determined, but an overview would suggest the risk of congenital damage is less than 10%, and probably less than 5%¹⁰. Maternal rubella reinfection with fetal infection and damage made a substantial contribution to the incidence of congenital rubella in the UK in the late 1980s and early 1990s¹⁰, but has declined as the incidence of rubella has fallen. Maternal reinfection with a rash is very rare, but can be presumed to present a significant, but not quantified, risk to the fetus as viraemia will have occurred.

The epidemiology of rubella in the UK has changed substantially since the introduction in 1988 of mumps, measles and rubella (MMR) vaccine for males and females in the second year of life, with an early 'catch-up' programme in preschool years and the measles/rubella vaccine campaign of 1994. Since the early 1990s, rubella has largely affected young adult males with only a few cases in pregnant women^{11,12}. The last case of congenital rubella (as of mid 2000) as a consequence of rubella acquired in England and Wales was in 1996 (personal communication, National Congenital Rubella Surveillance Programme), although one case occurred in Scotland in 1999¹³.

It is now more than 10 years since the report of the last Working Party which considered diagnosis of rubella¹, and the last guidance was issued in 1996⁴.

Parvovirus B19

There are a wide range of potential consequences of parvovirus B19 infection, ranging from minor febrile illness to erythema infectiosum (fifth disease or slapped cheek syndrome), generalised rash illness clinically indistinguishable from rubella, aplastic crises in patients with shortened red blood cell life, arthralgia, and persistent infection in the immunocompromised¹⁴. Infection in the first 20 weeks of pregnancy can lead to intrauterine death (risk 15% versus 5% in control group; excess risk 9%) and hydrops fetalis (risk 3%, if infection between 9-20 weeks gestation, and is included in the excess risk of 9%, of which about half die)¹⁵. These consequences usually occur some 3-5 weeks after the onset of maternal infection, but can be later. Permanent congenital abnormality has not been identified as a consequence of intrauterine infection, although persistent neonatal infection and anaemia can occur rarely¹⁶.

Parvovirus B19 reinfection and reactivation has been shown in volunteer studies¹⁷ and in the immunocompromised, but there is no evidence to suggest reinfection is a risk to the fetus.

Parvovirus B19 infection is common, with some 50% to 60% of adults having been infected¹⁸. No vaccine or preventive measures are available, and an increased incidence occurs every three to four years, largely in schoolchildren.

In 1998, guidance on the management of parvovirus B19 infection was issued by PHLS after consultation with a range of authorities². However, a number of areas in relation to management in pregnancy are outside the scope of that guidance.

Varicella-zoster virus

Disseminated primary varicella-zoster virus infection (chickenpox; varicella) presents as a characteristic vesicular rash, and clinical diagnosis is highly specific although not very sensitive as subclinical and mild cases occur. Infection during the first 20 weeks of pregnancy can lead to intrauterine infection with characteristic fetal damage in some 1%¹⁹. Maternal infection at 20-37 weeks gestation can lead to intrauterine infection and herpes zoster in childhood. Maternal infection with onset within one week pre- or post-delivery can lead to neonatal varicella, which is potentially life-threatening if untreated; the degree of risk cannot be quantified given that immunoglobulin prophylaxis and antiviral treatment is now accepted practice, and early studies, which showed a risk of up to 30%, are likely to have been biased by selective reporting.

Localised varicella-zoster virus infection (shingles; zoster) reflects reactivation of the latent virus, and is usually dermatome restricted. There is no observed risk to the fetus or neonate of localised maternal herpes zoster¹⁹, although it is uncertain whether dissemination of herpes zoster, as may occur in the immunocompromised, carries a fetal/neonatal risk.

Varicella-zoster virus reinfection has been described, but is rare²⁰.

Varicella-zoster is endemic in the UK, with some 90% of young adults having been infected²¹. An attenuated live varicella-zoster virus vaccine has been available for many years²². Its use on a named patient basis in the UK has been limited previously to specific groups at significant risk, primarily immunocompromised susceptible children.

Guidance on the management of varicella-zoster virus infection in pregnancy and the newborn was published in 1998³.

Measles

The clinical features and complications of measles in the child and adult are well established and include disseminated rash, coryza, conjunctivitis, pneumonia, otitis media, encephalitis, etc.²³ Infection in pregnancy can lead to intrauterine death and pre-term delivery²⁴, but is not associated with congenital infection or abnormalities.

Indigenous measles is rare in the UK following introduction of MMR vaccine in 1988 and the MR vaccine campaign of 1994²⁵ except in the unvaccinated or in communities with low coverage²⁶. Most cases are now noted in people who move to the UK from countries where measles is still endemic. Recent falls in vaccine coverage have contributed to a rise in susceptible individuals that may eventually accumulate to the point where epidemics will occur as seen in Dublin in 1999-2000²⁷. Human normal immunoglobulin (HNIG) may not prevent measles, but has been shown to attenuate the illness. There is no evidence that it prevents intrauterine death or pre-term delivery.

Enteroviruses

Enterovirus infection (coxsackievirus A, B; echovirus; enterovirus 68-71) may have a wide range of manifestations such as meningitis; hand, foot and mouth disease; febrile illness; myocarditis; and Bornholm disease. Infection during pregnancy is not associated with any particular fetal consequence, although rarely it can result in abortion (as can any febrile illness)²⁸. Neonatal infection is usually acquired from the mother or by cross-infection. Neonatal infection, particularly with selected echoviruses, can have multi-system life-threatening complications²⁹.

Sporadic enterovirus infection is not uncommon, but major summer epidemics have not been seen in the UK for some years. Except for poliovirus, no vaccines are available. Immunoglobulin has been advised for prophylaxis in exposed neonates²⁹.

Hand, foot and mouth disease is characterised by vesicular lesions of hand, feet and mouth; the latter soon break down to ulcers. It is a commonly recognised manifestation of enterovirus infection. Pregnant women presenting with the characteristic features may be investigated by viral cultures of faeces and throat swab (serology is of little value), but can be reassured that there is no adverse consequence for the fetus. Pregnant women in contact with cases of hand, foot and mouth disease should be reassured.

Infectious mononucleosis

Infectious mononucleosis (IM) is a common presentation of primary Epstein-Barr virus (EBV) in young adults. IM is characterised by generalised lymphadenopathy, fever, sore throat and typical haematological and serological findings, including the detection of heterophil antibody. A generalised maculopapular rash is an associated accompanying feature³⁰, particularly if ampicillin or a similar antibiotic has been taken.

Primary EBV infection in pregnancy (whether clinically apparent as IM or asymptomatic) carries no specific risk to the fetus³¹. EBV infection results in a latent infection with persistent excretion in the throat of a proportion (circa 20%) of individuals. Hence exposure to EBV can occur irrespective of whether the contact patient has IM; exposure to IM does not require investigation and the patient can be reassured. Some 50% of young adults are susceptible to EBV, with higher rates in more affluent social groups, and some 2% or more of those susceptible become infected annually. About 50% of these infections will present with IM.

Cytomegalovirus (CMV) can cause an IM-like syndrome with a generalised maculopapular rash, and must be considered if heterophil antibody is not detected. Primary infection with CMV may lead to intrauterine infection³². It is not considered further in these guidelines, as occurrence of a rash is very rare and no effective intervention exists.

The pregnant patient with a non-vesicular rash illness (algorithm 1)

Care must be taken in assessing the rash in a patient with a dark skin, as the appearance may not be typical of that seen in those with a lighter skin. Those whose first language is not English may not be familiar with common terms, such as 'chickenpox', and hence relevant history obtained must be interpreted with care. Patients who have spent their childhood years in other countries may not have had the same exposure to natural infection or vaccination opportunities as those brought up in the UK; consequently, the risk estimates presented here may not apply to these groups as they may have a higher or lower level of susceptibility.

Apart from varicella in the seven days before delivery, the infections which may have a specific impact on the fetus (rubella, parvovirus B19, varicella-zoster) only do so if infection occurs in the first 20 weeks of gestation. Hence, it is left to the managing clinician to decide whether investigation after 20 weeks is warranted, but it is strongly advised, irrespective of gestation, as:

- Specific diagnosis would help in managing potential risk to contacts, e.g. in health care situations such as GP surgeries and antenatal clinics (ANCs).
- It would provide information on the date of infection in relation to gestational age.
- The estimate of the gestation period may be wrong.
- The mother may be reassured that a specific diagnosis has been reached or excluded, and diagnosis may be helpful in the management of subsequent exposure.

Investigation will be directed by clinical/epidemiological information. A disseminated

vesicular rash is highly suggestive of varicella. The probability of streptococcal and meningococcal infection, measles, enterovirus, syphilis and infectious mononucleosis should be suggested by clinical features. Appropriate specific investigation and management should be instigated accordingly. Any doubt as to one of these diagnoses, or failure to confirm by laboratory investigation, must result in initiating investigation for rubella and parvovirus B19.

If features are compatible with rubella or parvovirus B19, appropriate laboratory investigation should be initiated, irrespective of past testing or immunisation. There is a remote possibility of past laboratory or documentation error, failed immunisation, symptomatic rubella reinfection or parvovirus B19 reinfection. It is recommended that, irrespective of a request for specific rubella or parvovirus B19 infection, all sera from women with rash illness are simultaneously investigated for both infections.

Current antibody detection techniques developed for use on saliva are not suitable for individual patient diagnosis in pregnancy.

The pregnant patient in contact with a rash illness (algorithms 2A, B and C)

'Contact' is defined as being in the same room (e.g. house or classroom or 2-4 bed hospital bay) for a period of 15 minutes or more, or face-to-face contact. This definition is based on experience with VZV exposure and errs on the side of caution. This definition of contact is probably sensible for all nosocomial exposures. In community exposures, which are probably more frequent and less likely to be well defined, it may be more practicable to apply a longer duration for the definition of contact, especially for parvovirus B19 infections where household exposure is overwhelmingly the most important source of infections in pregnancy (followed by intense occupational exposure).

If the rash in the contact is vesicular (varicella), see the later section on 'Management of vesicular rash'.

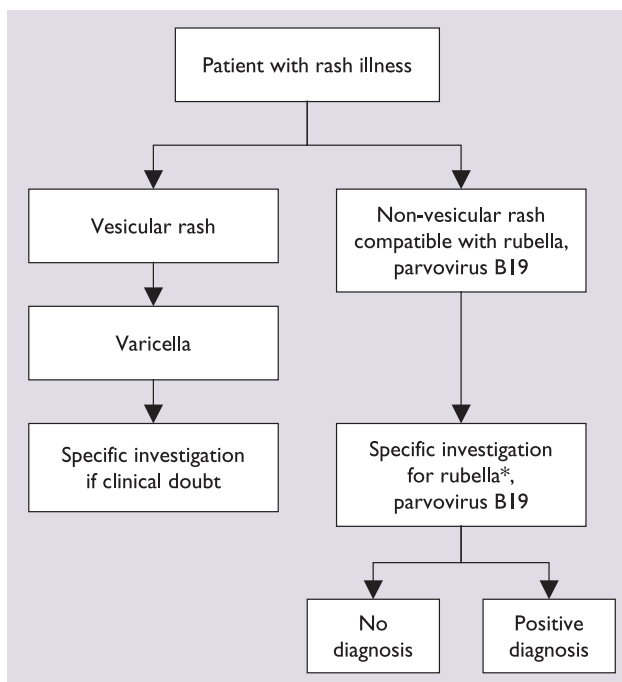
The aetiology of the rash in the contact may be diverse, and include non-infective causes. The possible causes which warrant consideration include measles, rubella and parvovirus B19. Other possible infective causes in the contact (e.g. enterovirus) should await development of illness in the pregnant woman. Investigation is recommended for rubella and parvovirus B19 in all cases, unless there is a strong reason to suspect measles and susceptibility to rubella is unlikely.

Rubella

If a woman has had one of the following, she should be reassured that the likelihood of rubella is extraordinarily remote, that specific rubella investigation is not required, but to return if a rash develops:

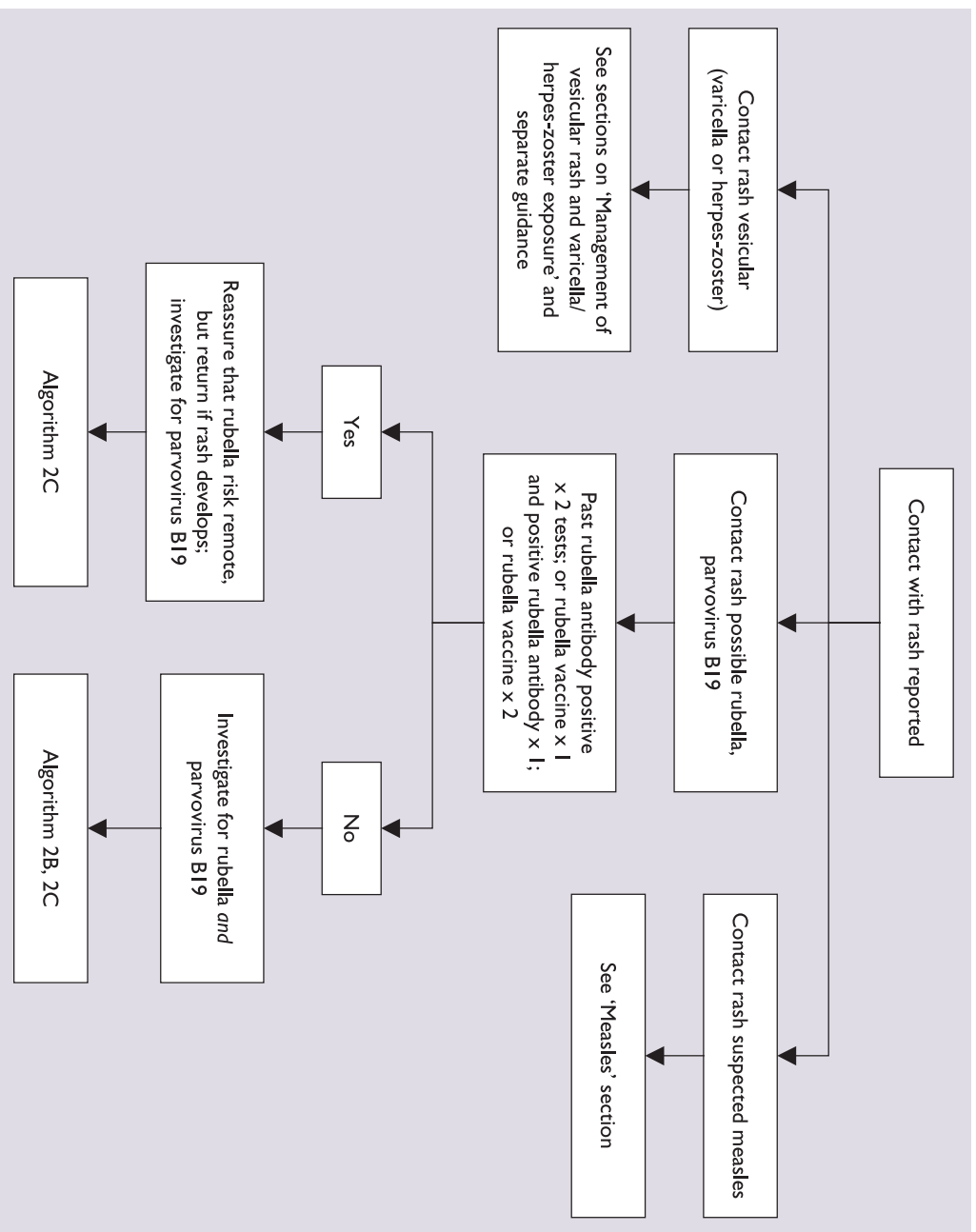
- at least two previous rubella antibody screening tests which have detected antibodies;
- at least two documented doses of rubella vaccine;
- one documented dose of vaccine followed by previous rubella antibody screening test which has detected antibodies.

ALGORITHM 1 Pregnant patient with rash illness

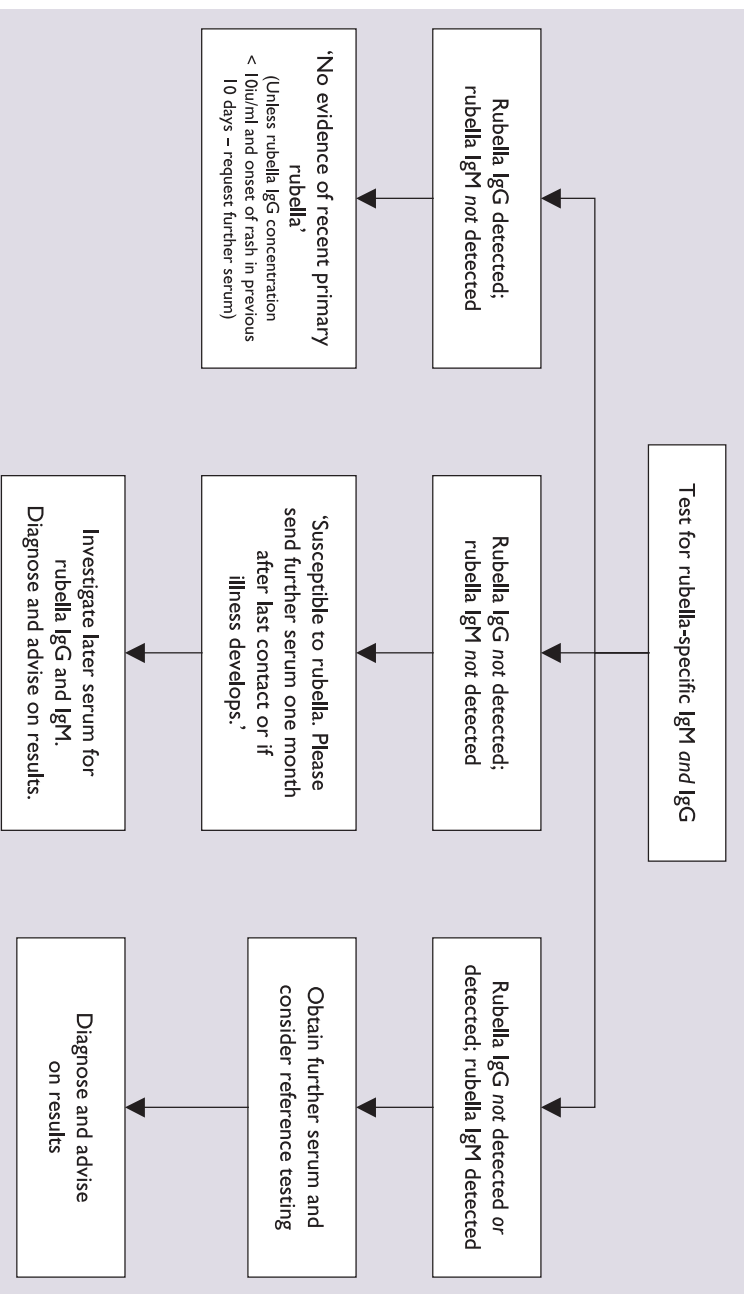


* Irrespective of past testing or immunisation

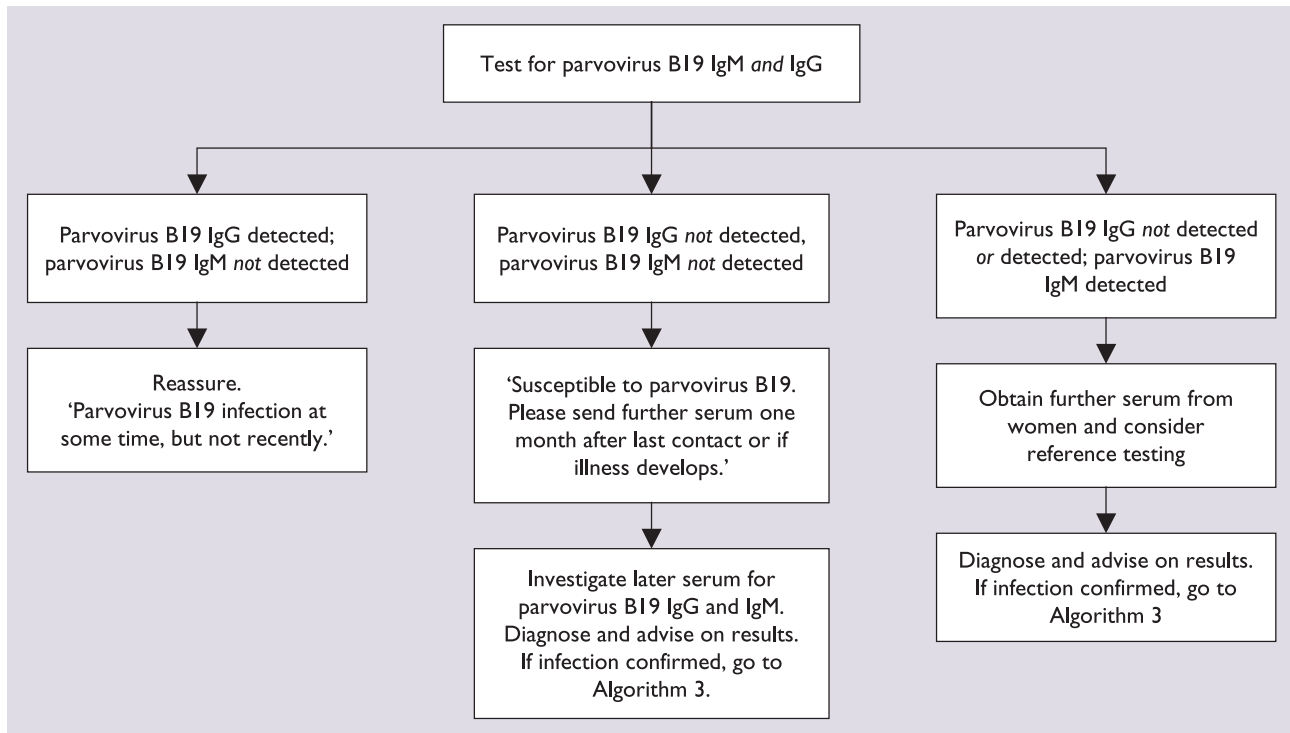
ALGORITHM 2A Pregnant patient who has been a contact of a person with rash illness



ALGORITHM 2B Investigation for rubella of pregnant woman with significant exposure to rash illness



ALGORITHM 2C Investigation for parvovirus B19 of pregnant woman with significant exposure to rash illness



If rubella susceptibility is possible (criteria above not present), a serum should be obtained as soon after contact as possible. (Full details must be given on the laboratory request form, as listed under 'Background' above, to ensure correct interpretation of results.)

The laboratory should simultaneously test for rubella-specific IgG and IgM, and the advice given in algorithms 2A and 2B should be followed. If rubella-specific IgG is detected, and rubella-specific IgM is not detected, women should be reported as 'no evidence of recent primary rubella'. There may be rare occasions when detection of rubella-specific IgG may precede by one to two days the development of specific IgM in the evolution of the antibody response in primary rubella. In a pregnant patient with onset of a rash in the previous 10 days, if a low concentration (say <10iu/ml) of rubella-specific IgG is detected, a further serum should be requested even if a rubella-specific IgM is not detected.

Active investigation for reinfection by obtaining and testing later sera is not indicated, given the low incidence of rubella in the UK (and hence unlikelihood that the contact had rubella) and the low risk to the fetus of reinfection in the absence of a maternal rash.

If rubella-specific IgM reactivity is detected, similar caveats as to the specificity of this result, and procedures to be followed, are as detailed in the section on 'Laboratory investigation of rubella' below.

Parvovirus B19

The pregnant woman should be investigated for asymptomatic parvovirus B19 infection (algorithms 2A, C), and investigation should not be delayed to ascertain if symptomatic infection occurs. This is because:

- Maternal asymptomatic parvovirus B19 infection

is at least as likely to infect and damage the fetus as symptomatic infection¹⁵;

- Active management of the infected fetus may reduce the risk of adverse outcome³³ (see 'Laboratory investigation of parvovirus B19' below).

Serum should be collected as soon after contact as possible and submitted to the laboratory with full clinical and epidemiological details (see 'Background' section). Investigating for asymptomatic parvovirus infection was not endorsed by the Public Health Medicine Environment Group.

Serum should be tested for both parvovirus B19-specific IgG and IgM. If specific IgG is detected (circa 50% probability), but specific IgM not detected, the woman should be reassured, and a report issued as 'parvovirus B19 infection at some time, but not recently'. If specific IgM is detected, but specific IgG not detected, a further serum should be collected and tested immediately. If specific IgG or IgM are not detected, further serum should be collected and tested one month after last contact. If, after testing one month later, specific IgG and IgM are not detected, the woman should be reassured and a report issued as 'no evidence of recent parvovirus B19 infection, but is susceptible'.

Measles

If the source patient is suspected as having measles based on epidemiology and clinical features, consideration should be given to passive prophylaxis with intramuscular human normal immunoglobulin (HNIG) as soon as possible after exposure, but within six days³⁴. There is no evidence that post-exposure prophylaxis with HNIG confers any benefit for the

fetus, although it may attenuate maternal illness. Clinical features suggestive of measles are described in 'Specific infections' above. Additional factors that would increase the likelihood of measles are as follows.

- The rash contact took place when the woman was abroad.
- The contact had travelled abroad.
- The contact has not received measles vaccine in the past (such as MMR).
- The contact has been hospitalised recently.
- The contact is linked epidemiologically to a confirmed measles case.

If the woman has received two doses of measles vaccine in the past, in view of the low incidence of measles infection in the UK, she should be reassured as to the low probability of her becoming infected. If there is no or poorly documented history of vaccination, serum should be collected and administration of HNIG should await an urgent determination of measles-specific IgG (available through a local laboratory). If measles-specific IgG is detected within 10 days of contact (>95% probability of being 'immune' in the UK and particularly if born before 1970) further action is unnecessary. Failure to detect measles-specific IgG would warrant administration of HNIG, and serological follow-up three weeks after last contact: HNIG may attenuate but not prevent measles. If contact was more than 10 days prior to presentation, serum should be collected and stored. Management would be expectant and specific measles serological investigation only performed if rash illness develops.

Laboratory investigation

Rubella

The routine antenatal testing for rubella antibody is for determining susceptibility and identifying those for whom vaccine is advised post delivery; it does not determine whether rubella may have occurred in the current pregnancy. If such investigation is required, the request form must clearly state that recent rubella is a possibility, and full clinical and epidemiological details must be given (see 'Background' section above).

The serological diagnosis of rubella is well established³⁵. A serum at first presentation must be collected and sent for laboratory testing.

It is recommended that the laboratory investigate all cases of possible rubella by simultaneous testing for rubella-specific IgG (or total rubella antibody) and IgM. When reporting the results of rubella serology, the laboratory must advise on any further sera/follow-up required, and give a definitive conclusion of their investigations, e.g. 'no evidence of recent primary rubella'.

Problems arise when investigation commences four weeks or more after the onset of rash illness. If rubella-specific IgG is detected, and specific IgM is not detected, rubella as a cause of the rash illness cannot be excluded serologically unless past sera can be tested to determine whether seroconversion has occurred recently. An assessment of probabilities has to be made based on recent epidemiology of rubella in the

community, past history of vaccine and testing, characteristics of illness, etc.

Some women present significant problems in diagnosis, particularly in those who give a positive result for rubella-specific IgM. Although positive rubella IgM results which do not reflect recent rubella (primary or reinfection) ('false positive') are infrequent, the control of rubella in the UK means that most rubella-specific IgM positive results do not reflect recent rubella. No woman in the first 20 weeks of pregnancy should have rubella diagnosed based on a positive rubella-specific IgM alone. Results must be interpreted in relation to full clinical and epidemiological information. Unless seroconversion has been shown, further testing by alternative rubella-specific IgM tests and measuring the strength of binding of specific IgG (avidity)³⁵ is advised. IgG avidity is low soon after a primary infection, but matures over a few weeks to become more strongly binding. If rubella-specific IgM positivity reflects a recent rubella episode (whether primary or reinfection), the degree of reactivity will usually change over the period of a few weeks, rather than persisting at a similar level.

Parvovirus B19

Recent parvovirus B19 infection can be confirmed or excluded by testing for parvovirus B19 specific IgM on the first serum obtained. Failure to detect parvovirus B19 specific IgM excludes infection in the four weeks prior to collection of the serum. Hence, infection cannot be excluded if investigation commences more than four weeks after onset of rash illness (see 'Rubella' above).

If parvovirus B19 IgM is detected in the first 20 weeks of pregnancy, confirmation is required by an alternative assay, e.g. M-capture RIA, IgM specific immunofluorescence or IgG seroconversion using an antenatal booking blood. Repeat testing will demonstrate a decline in IgM reactivity and provide an additional confirmation method.

Hydrops fetalis

In a pregnant woman presenting with hydrops fetalis without a rash history, the diagnosis of recent parvovirus B19 infection can only sometimes be achieved by testing for parvovirus B19 specific IgM, as the acute infection was usually some weeks prior to presentation. Infection with parvovirus B19 as the cause of hydrops fetalis can be investigated by testing the antenatal booking sample in parallel with the sample at presentation for parvovirus-specific IgG to show seroconversion.

Following confirmation of parvovirus B19 in a pregnant woman presenting with hydrops fetalis, referral to a Regional Unit of Fetal Medicine is recommended if this has not already occurred. If a fetal blood sample is collected, then examination by molecular methods (PCR or dot blot hybridisation) and/or electron microscopy for parvovirus B19 virus particles to confirm fetal infection can be arranged by Virology Laboratories.

Proven parvovirus B19 infection in the hydropic fetus will influence the management of the patient, as it is important in establishing the aetiology of the hydrops and in excluding other causes so allowing appropriate counselling of the patient.

Management

Management of proven infection

Rubella – primary and reinfection (table 1)

The management of primary rubella or symptomatic rubella reinfection would depend on the gestation of pregnancy at which rubella occurred, and the individual circumstances of the woman. If a case of asymptomatic rubella reinfection is identified or suspected, management would, as for primary rubella, depend on the gestation of pregnancy and the individual circumstances of the woman. Given the low but definite risk to the fetus of maternal rubella reinfection in the first 16 weeks of pregnancy, there may be occasions when consideration is given to further fetal investigation by genome detection to ascertain if fetal infection has occurred. A range of possible approaches has been explored, but they are all invasive (e.g. amniocentesis, fetal blood sampling) and carry a risk of adverse outcome.

The necessary virological techniques for fetal investigation are neither validated nor available in the UK, and laboratory-based members of the Working Group should be consulted for advice if such approaches are being considered; it is strongly advised that management is based on risk assessment.

Parvovirus B19 (algorithm 3)

The management of proven parvovirus B19 infection has become more active with the demonstration that intrauterine transfusion of the fetus improves the outcome³³. The following management is suggested.

- On diagnosis of parvovirus B19 infection, ultrasound scanning of the fetus is started 4 weeks post onset of illness or date of seroconversion, and then at 1-2 weekly intervals until 30 weeks gestation.
- If findings suggestive of hydrops fetalis, or its development, are found, the patient should be referred to a Regional Unit for Fetal Medicine for consideration of fetal blood sampling and intrauterine transfusion.

Further techniques are becoming available which may assist in fetal assessment. These include Doppler assessment of the middle cerebral artery for anaemia and parvovirus B19 genome detection in amniotic fluid.

Measles, enterovirus, infectious mononucleosis

The management of the pregnancy in these infections is expectant, although follow-up of the infant should be considered even though no congenital infection and damage would be anticipated.

The 'continuously exposed' female in the first 20 weeks of pregnancy (e.g. schoolteacher)

Exclusion is not recommended of pregnant women susceptible to rubella or varicella-zoster from

environments which may suggest a higher rate of exposure (e.g. schoolteachers). Rubella is now rare in children, and exposure to varicella-zoster is as likely to occur in the wider community.

Guidance on the management of pregnant women susceptible to parvovirus B19 has recently been published².

Screening for rubella antibody

Frequency of testing

It is likely that, given the current low incidence of rubella in the UK, the cost benefit of the current rubella antibody screening strategy will be reviewed by the National Screening Committee at some stage.

The advice regarding frequency of testing given in 'Immunisation against infectious disease'⁴ is appropriate. This advice states: 'Women should be screened for rubella antibodies at least in the first pregnancy, irrespective of a previous positive rubella antibody result. Very occasionally, laboratory errors or errors during reporting may result in patients who are rubella antibody negative being reported as rubella antibody positive. When there are documented results available of two tests using a specific method, both confirming the presence of rubella antibody, then further screening in pregnancy is unnecessary unless contact with suspected rubella or a rubella-like rash occurs.'

This guideline does update the above advice, however, in recommending that further testing is not required if contact with suspected rubella or rubella-like rash occurs (see section on 'Contact with rash illness' above).

Primary and secondary care NHS Trusts are recommended to review their compliance. It is appreciated, however, that a pragmatic and cost-efficient balance has to be drawn locally between screening every woman in every pregnancy and selective screening based on documented results.

Laboratory guidance

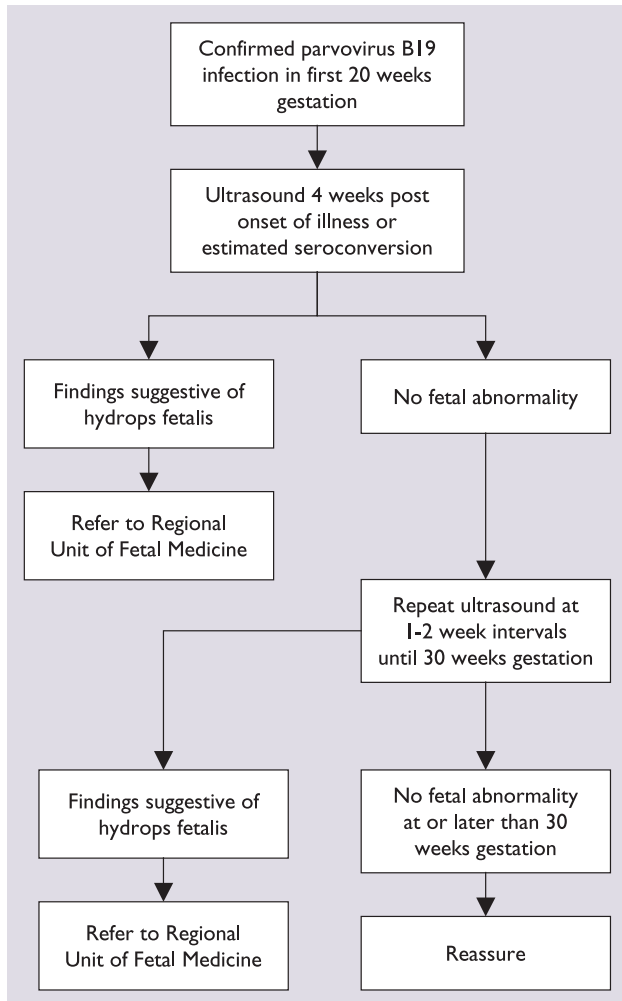
A number of reliable and validated assays are available for rubella antibody screening, such as enzyme-linked immunosorbent assays (EIA), radial haemolysis (RH), and latex agglutination (LA). The cut off concentration of 15 international units (iu)/ml traditionally used in the UK was based on the lack of specificity of the haemagglutination inhibition (HI) test at low concentration of antibody. Many commercial EIAs have a cut off of approximately 10 iu/ml and such a cut off may be accepted as valid, providing the assay is continuously monitored by the use of a second confirmatory assay as described below. This has been endorsed in the USA³⁶.

Sera giving <10 iu/ml in the first assay should be retested, from the clot if available, to exclude laboratory error on first testing, validate the assay run, and, if an alternate assay is used, identify sera with low but detectable rubella antibody. If sera negative on first testing are found positive on further testing, the serum should be retested in the original

TABLE 1 Characteristics of rubella, parvovirus B19 and varicella-zoster virus infections in UK

	Rubella	Parvovirus B19	Varicella-zoster
Proportion susceptible in young adult females	1-2%	40-50%	10%
Infectivity - risk of transmission from close contact (household attack rate)	High (90%)	Medium (50%)	High (70-90%)
Risk of intrauterine transmission by (gestational age)	< 11 weeks - 90% 11-16 weeks - 55% > 16 weeks - 45%	< 4 weeks - 0% 5-16 weeks - 15% > 16 weeks - 25-70%, increasing with gestation	< 28 weeks - 5-10% 28-36 weeks - 25% > 36 weeks - 50%
Risk of adverse fetal outcome	< 11 weeks - 90% 11-16 weeks - 20% 16-20 weeks - minimal risk of deafness only > 20 weeks - no increased risk	< 20 weeks - 9% excess fetal loss; 3% hydrops fetalis, of which about 50% die	Congenital varicella syndrome: < 13 weeks - 1% risk, 13-20 weeks - 2% risk. 4 days prior to 2 days post delivery - 20% neonatal varicella
Risk of adverse outcome for mother	Arthritis	Arthritis	Pneumonitis. Case fatality rate for mother estimated at 1/1000 infections in pregnancy
Interventions and benefit	Termination of pregnancy	Fetal hydrops - intrauterine transfusion reduces odds of death to 0.14	VZIG to mother and neonate attenuates illness; Aciclovir within 24 hours of rash onset for mother; Aciclovir for infected neonates
Incubation period	14-21 days	13-18 days	14-21 days
Infectivity period (days pre and post rash onset)	7 days pre to 10 days post onset of rash	10 days pre to day of onset of rash	2 days pre onset of rash until crusting has ceased and all lesions crusted
Number of infections in pregnancy	Currently rare	1 in 400 pregnancies (ref 18) or seroconversion of 1.5-13% per annum among susceptible	Exposure use of VZIG: 590-785 women per year, 1996-99, England and Wales. (Estimate 2-3 infections per 1000 pregnancies or 2000 maternal infections per year)
Terminations of pregnancy	1995-96 - 18 cases 1997 - 2 cases	Unknown - not recommended	Unknown
Babies with congenital infection (proven)	1994-96 - 20 cases 1997 to date - 1 case	Unknown	Unknown
Babies with congenital damage (proven)	1994-96 - 19 cases 1997 to date - 1 case	Unknown	Unknown
Babies with congenital infection (estimate)	Rare (see text)	See below	30 neonates at risk of severe neonatal infection per year in UK
Babies with congenital damage (estimate)	Rare (see text)	2-8 fetal hydrops per 100,000 pregnancies (14-56 cases per year in UK). 12-48 per 100,000 spontaneous abortion (84-336 cases per year in UK).	10 per year, England and Wales

ALGORITHM 3 Management of confirmed parvovirus B19 infection in pregnancy



assay. If positive on retesting, consideration should be given to retesting the batch to exclude serum transposition (i.e. another serum has been falsely identified as positive).

Given the sensitivity and specificity of EIA, RH and LA, if rubella-specific IgG can be detected by repeat testing in a validated assay or in two or more validated assays at whatever the concentration, the woman should be reported as 'rubella antibody detected'. This approach would result in almost all those screened being reported as 'rubella antibody detected', or 'rubella antibody not detected' with advice being given 'rubella immunisation advised (post-delivery if pregnant)'.

There may be exceptionally rare instances where further reference testing may be indicated, for example where variable results are obtained on retesting and where there is a documented history of multiple doses of vaccine yet rubella-specific IgG cannot be detected on local testing.

If rubella-specific IgG is not detected, yet the woman has received two or more documented doses of rubella vaccine, further doses of vaccine are unlikely to be of value and protection against primary rubella assumed, although such women should be advised to report any rash illness.

Parvovirus B19 antibody screening

Unselected screening of pregnant women for past infection with parvovirus B19 is not recommended as no vaccine or prophylaxis are available. This advice will need reconsideration if a licensed vaccine becomes available.

Management of vesicular rash (varicella) in pregnancy

Management has to take into account the possible effect on both mother and fetus.

The mother

Pregnant women should be advised to consult their general practitioner at the first sign of varicella. They should avoid contact with others who might be at risk, such as other pregnant women and neonates.

The diagnosis can be made clinically in many instances, but if there is doubt, confirmation of varicella should be sought by virus, antigen or genome detection in vesicle fluid and urgent serology for the presence of VZV IgM.

The time of onset of the rash is important for determining the likely effectiveness of antiviral treatment. Onset is timed from the first observable lesion. If the woman presents within 24 hours of the onset of the rash, she should be offered oral antiviral treatment for seven days (aciclovir) (with informed consent). If it is more than 24 hours from the onset of rash, then antivirals are not advised as there is no evidence that they would alter the natural history in the uncomplicated case³⁷.

If the varicella is uncomplicated, then the woman can be reassured and sent home for daily review or to be seen earlier if she deteriorates. If there is no deterioration but fever persists, or the cropping of the rash continues after six days, the woman should be referred for urgent hospital assessment.

The general practitioner will need to decide whether their patient can be managed in the community or whether she needs hospitalisation. The criteria indicating that hospitalisation is required are³:

Absolute indicators

- chest symptoms;
- neurological symptoms other than headache;
- haemorrhagic rash or bleeding;
- severe disease - dense rash/numerous mucosal lesions;
- significant immunosuppression.

Contributory factors

- pregnancy approaching term;
- bad obstetric history;
- smoker;
- chronic lung disease;
- poor social circumstances;
- GP unable to monitor patient closely.

The woman needs to be assessed when she presents, and if she shows evidence of severe disease at that stage or subsequently, she should be referred immediately for urgent assessment in a specialist isolation facility where she has access to the expertise of an obstetrician, infectious disease specialist and

paediatrician. Women who appear to have uncomplicated infections must be monitored closely for deterioration.

If severe disease develops and hospitalisation is necessary, the woman should be treated with intravenous aciclovir (10 mg/kg tds for five days at least).

The fetus

The effect of maternal infection on the fetus or neonate depends on the timing of the infection. The risk of congenital varicella syndrome is some 1% in the first 12 weeks, and around 2% between weeks 13-20 of pregnancy. Infection from the beginning of the second trimester up to one week from delivery may lead to herpes zoster in an otherwise healthy infant. Infection from one week before to one week after delivery can lead to severe neonatal varicella.

Management of varicella/herpes-zoster exposure in pregnancy

Women who are exposed to varicella or herpes zoster in pregnancy should seek medical attention as soon as possible.

A significant contact is defined as being in the same room (e.g. house or classroom or 2-4 bed hospital bay) for a significant period of time (15 minutes or more) or face-to-face contact.

If the woman has a history of varicella or zoster, protection can be assumed and reassurance given.

If there is no history of past varicella or zoster, the woman's susceptibility should be determined urgently, and if they are varicella-zoster IgG negative then they may be offered VZIG if they are within 10 days of the exposure²¹. For continuous household exposure (for example when a child in the household is infected), VZIG should be offered within 10 days of the onset of rash in the index case.

Aciclovir is not licensed to be used prophylactically and so cannot yet be recommended for this purpose.

Management of neonate exposed to varicella/herpes-zoster

Infants whose mothers develop varicella in the 7 days before to 7 days after delivery and VZ antibody negative infants who are exposed to varicella or herpes zoster in the first 7 days of life should be given VZIG. Exposed infants born before 28 weeks gestation or weighing less than 1000 g should be given VZIG, as transfer of maternal IgG antibodies may be inadequate¹⁹. Some infants more than 28 weeks gestation at birth may be VZV antibody negative if they are more than 60 days old or have had repeated blood samples, despite a maternal history of varicella or zoster¹⁹; serological testing of such infants is recommended.

If severe varicella develops despite VZIG, high-dose intravenous aciclovir treatment should be started as soon as possible. Prophylactic intravenous aciclovir should be considered for infants whose mothers develop varicella four days before to two days after

delivery as they are at highest risk of fatal outcome despite VZIG prophylaxis.

Mothers with varicella should be allowed to breast feed. If they have lesions close to the nipple, they should express milk from the affected breast until the lesions have crusted; this expressed milk can be fed to the baby if he/she is covered by VZIG and/or aciclovir.

If other children in the family have varicella, and the mother has had varicella or has been shown to have varicella-zoster virus antibody, then there is no reason to prevent a new baby going home. If the mother is susceptible, contact with siblings with varicella should be delayed until the new baby has reached seven days of age.

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