Investigating the pregnant woman exposed to a child with a rash

The author explains what action to take after exposure of a pregnant woman to a child with a rash, to reduce the risk of adverse outcomes for mother and child

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A 21 year old woman attending a routine antenatal appointment 38 weeks into her pregnancy mentions that her child, a toddler, has been ill. He was diagnosed with chickenpox nearly a week ago when his father took him to the emergency department with an itchy rash and high temperature. He is now better and the spots have all dried up and crusted over. On questioning, the patient is unsure if she herself has ever had chickenpox or shingles, or if she has received any doses of varicella vaccine. She is not aware of the risks of varicella to herself or to her unborn child. Her child has received all the recommended immunisations, but this does not include varicella vaccine in the area where they live.

What is the challenge?

When a pregnant woman is exposed to a child with a rash, the situation requires rapid assessment. The rash could be due to any one of several infectious or non-infectious causes, but the initial approach needs to focus on those infections that pose risks to the mother and fetus or neonate, and for which intervention can improve the outcome.1 These infections are measles, rubella, parvovirus B19, and varicella zoster virus (table 1).2

Measles warrants consideration in endemic regions (such as Europe and Africa) or in association with an imported outbreak.2 Even minimal exposure to a putative case warrants careful assessment in view of the notorious transmissibility of measles.3 Congenital rubella continues to be reported from countries with measles, mumps, and rubella (MMR) vaccination programmes, and cases can occur after subclinical maternal re-infection.1 4 5 Fifty per cent of pregnant women remain susceptible to parvovirus B19, and subclinical infection is common.6 7 Varicella remains a substantial risk to pregnancy, with rates of susceptibility among pregnant women ranging from 10% in temperate countries (such as Belgium and Ireland) to 50% in tropical or subtropical climates.8

What do we need to know?

Investigation is based on the collection of accurate information about the illness in the putative index case; the nature, timing, and duration of exposure; and the woman’s susceptibility (box 1).

Exposure to varicella has been defined as face to face contact or 15 minutes in the same room.9 The same criteria can be used for rubella and parvovirus, but lesser exposure to measles may be relevant.1 7 Household exposure is associated with a high risk of transmission.1

What type of rash does the index case have?

Dependable information about the child’s rash can help narrow the possibilities (table 2). If the rash is maculopapular, consider measles, rubella, and parvovirus B19. If it is vesicular, the assessment can be limited to varicella zoster virus (figure 1).

Attempt to secure a laboratory diagnosis for the child where feasible, in parallel with the immediate assessment of the woman’s susceptibility.1

Maculopapular rash

If a maculopapular rash was present in the index case, measles is the most urgent consideration, because immunoglobulin needs to be administered within six days of exposure. Serological testing of the index case may be helpful, but the timing is tight, as measles IgM may not appear in serum until five days after onset of the rash (table 2).

Measles or rubella in the index case can be diagnosed by nucleic acid amplification technology (NAT) testing of a saliva or throat swab, collected in the early days of the rash.1 2 5

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Parvovirus IgM is usually detectable at the onset of rash in symptomatic cases. A positive result requires confirmation (table 2).

**Vesicular rash**
If the diagnosis is uncertain, chickenpox or shingles can be confirmed in blister material scraped or swabbed from a disrupted skin lesion. The choice of test depends on the available technology. NAT testing is specific and sensitive (both approaching 100%), and can detect varicella zoster virus DNA in crusted lesions deemed to be no longer infectious (table 3). Older technologies, including rapid antigen detection, Tzanck smear (for presence of multinucleate giant cells), and electron microscopy, are more dependent on the quality and timing of the sample and rely on the skill of the microscopist. Positive Tzanck or electron microscopy tests do not differentiate between varicella zoster virus and herpes simplex virus in blister material.

**What tests does the pregnant woman need and how should the results be interpreted?**
If reliable information about the contact is not available, maternal susceptibility to infection with all four viruses, as outlined below, will need to be assessed. It is advisable to seek local virology, microbiology, or infectious diseases advice straight away to expedite initial testing and follow-up.

**Exposure to a maculopapular rash**
Assess the woman’s rubella and measles status on the basis of the available information (box 1). For measles and rubella, previous MMR vaccination or previous positive IgG test results can provide satisfactory evidence of immunity. For parvovirus B19, however, serological testing is essential unless another diagnosis has been confirmed in the child (table 3).

**Measles**
If the woman has evidence of immunity (table 3), laboratory testing is not necessary. If her status is unknown, request a measles IgG test. If this test is negative, human normal immunoglobulin may prevent or attenuate maternal measles.

Since immunoglobulin needs to be given within six days of exposure, it may not be possible to establish the woman’s measles IgG status in time. A sample should nevertheless be secured for subsequent testing. If the woman has a negative measles IgG result or her status remains unknown the decision to give prophylactic immune globulin will rest on a risk assessment of the likelihood of measles exposure, with advice from the local public health service.

**Rubella**
If immunity is in doubt, the woman should be tested for rubella IgG and IgM. The IgG test should be a quantitative assay with results reported in international units/mL (IU/mL). Rubella susceptibility is defined as an IgG level of less than 10 IU/mL. If the IgG test is positive (>10 IU/mL) and IgM is not detected, reassure the patient. If rubella serology is negative—that is, neither IgG nor IgM is detected—repeat the tests. The repeat testing should be done after an interval of at least one month following the most recent exposure. If rubella IgM is detected, either in the initial test or after further testing, regardless of the IgG result, take a repeat sample and seek specialist advice without delay.

**Parvovirus B19**
Unless an alternative diagnosis has been confirmed in the putative index case, test the pregnant woman for parvovirus B19 IgG and IgM (table 3). If parvovirus IgG is detected and IgM is not detected, and the patient presented within a month of exposure, she can be reassured. If both IgG and IgM are negative, repeat the tests. The repeat testing should be done when at least one month has elapsed since the most recent exposure. If parvovirus IgM is detected on either occasion, regardless of the IgG result, take a repeat sample and seek specialist advice without delay. In cases of maternal parvovirus B19 infection, close monitoring for hydrops fetalis and the need for intrauterine transfusion is required.

**Exposure to a vesicular rash**
Assess the woman’s varicella zoster virus status, to facilitate timely administration of post-exposure prophylaxis with
varicella zoster immune globulin (VZIG) if she is susceptible (box 1, table 3).

A woman who has received two doses of varicella vaccine can be judged to be protected from chickenpox. Likewise, a history of chickenpox (or shingles) has a high positive predictive value for immunity in temperate countries, such as Belgium and Ireland, where the adult seroprevalence is over 90%. In the case of a pregnant woman raised in tropical or subtropical climates, however, where the mean age of infection is in early adulthood (such as sub-Saharan Africa, South India, and the West Indies), history may be less reliable. Consider post-exposure testing in these circumstances, regardless of history.

If, as in the present case, the woman is unsure, or gives a negative history of chickenpox, test for varicella zoster IgG. A negative history of chickenpox is unreliable; most women who give such a history are varicella zoster virus IgG-positive on testing.

Many commercial tests for varicella zoster virus IgG have suboptimal sensitivity—sometimes less than 70%—so it is important to tell the laboratory the reason for testing, to ensure that the most appropriate test available is used. Work is currently underway to improve the sensitivity and specificity of IgG tests and to define antibody cut-off levels for varicella zoster virus susceptibility.

The main rationale for administration of VZIG is to ameliorate or prevent severe maternal chickenpox and reduce the risk of maternal death.

Fifty percent of susceptible pregnant women given VZIG after household exposure still developed chickenpox, while 25% seroconverted with subclinical infection. The limited available evidence does not show whether VZIG can reduce the risk of congenital varicella. In one study, however, the risk of congenital VZV infection following maternal chickenpox was significantly lower in women who had received VZIG than in those who did not.

The recommended time frame for giving VZIG varies. US guidance advises giving VZIG within 96 hours of exposure, but in the UK, VZIG can be given to a household contact within 10 days of onset of the rash in the index case. The UK policy is based on data showing comparable rates of prevention, or attenuation of disease, when VZIG is given up to 10 days post exposure.

If the IgG result will not be available in time, the decision about giving VZIG needs to be made on an individual case basis with advice from infection experts. Whether or not she receives VZIG, the woman should be advised to make immediate contact if she develops symptoms of a rash illness.

Laboratory testing service

Accurate clinical information must be provided with the sample to optimise laboratory investigations. If the woman presents within a day or two of exposure, and if the testing laboratory has short turnaround times for urgent samples, it should be possible to obtain results in time to provide prophylaxis if needed. Even if test results cannot be obtained in time to inform the decision, the test should still be done. Testing can be greatly expedited if antenatal booking blood samples are routinely stored in the laboratory, where only a telephone call to the laboratory is needed to trigger determination of immune status. The availability of a stored booking sample can also help expedite diagnosis by showing IgG seroconversion, which is especially useful in asymptomatic infection or if the exposure is not reported for several weeks.

When is specialist referral needed?

Inform the patient’s obstetric care providers of any IgG seronegative result on initial testing for any of the four agents, and refer to a specialist if the mother develops a rash illness or has a positive rubella or parvovirus IgM test result. Make decisions about management—including administration of post-exposure prophylaxis and the conduct of further investigations and interventions—together with obstetric carers supported by specialist virology, microbiology, or infectious diseases expertise.

Case outcome

The patient tested negative for varicella zoster virus IgG and received VZIG seven days after onset of her child’s rash. She went into labour at 39 weeks, two days, and delivered a healthy male infant. Three days later, however, after discharge from hospital, she developed chickenpox lesions. She was treated orally with valaciclovir. VZIG was administered to her infant son to prevent neonatal varicella. Prophylactic intravenous acyclovir was considered for the child but was not administered. He was carefully monitored and did not develop signs of infection. Both mother and baby are well, and steps were taken to reduce the mother’s risk of infection in future pregnancy (box 2).

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Box 2 Reducing risk of infection in future pregnancy

As prevention is better than post-exposure prophylaxis, take these steps to reduce risk

**Planned pregnancy**
- Check history of varicella or shingles and establish measles, rubella, and varicella vaccination status before planned pregnancy. Test IgG to check susceptibility if necessary. Postpone pregnancy pending vaccinations if tests are negative

**Booking**
- Ask about and record the woman’s vaccination status and history of chickenpox or shingles
- Include rubella IgG status in routine antenatal screening
- Consider measles IgG and varicella zoster virus IgG testing if she does not have evidence of protection and might be at risk of exposure
- Request routine storage of antenatal booking serum samples after routine infection screening

**General advice**
- Tell pregnant patients to avoid contact with rash illness and to report any exposure as soon as possible and by telephone, rather than in person

**Post partum**
- Review women found to be seronegative for measles or rubella during pregnancy; advise postponement of further pregnancy pending vaccination
- Review women who are found to be seronegative for varicella zoster virus during pregnancy, but who did not develop chickenpox. Re-test if VZIG was administered. Advise postponement of further pregnancy pending appropriate vaccination for those remaining seronegative

**Learning points**
- Appropriate action after exposure of a pregnant woman to varicella zoster virus, measles, rubella, or parvovirus B19 can reduce the risk of adverse outcomes for the mother and child
- Rapid assessment, with information on the illness in the index case, timing and duration of exposure, and pregnant woman’s susceptibility are critical in determining the level of risk, tests required, and further management
- After exposure to a maculopapular rash illness, always test for parvovirus IgG and IgM, unless an alternative diagnosis has been confirmed by laboratory testing of the index case
- The antenatal testing laboratory may routinely store antenatal blood samples, which can facilitate urgent testing for susceptibility
- Seek specialist advice after rash exposure in pregnancy if the woman does not have satisfactory evidence of immunity and requires intervention or further testing. Women with clinical or laboratory evidence of current or recent infection should likewise be referred
## Tables

Table 1: Risk of maternal infection to the mother and to the fetus or neonate

<table>
<thead>
<tr>
<th>Risk to susceptible mother</th>
<th>Timing of maternal infection and risks to fetus or neonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella zoster virus</td>
<td></td>
</tr>
<tr>
<td>Chickenpox</td>
<td>0-20 weeks: congenital varicella (0.4-2.0%)</td>
</tr>
<tr>
<td>Severe or fatal pneumonia in pregnancy, especially in latter half of pregnancy; fatality rate 5 times that in other adults</td>
<td>13-40 weeks: shingles in infancy (1-2%)</td>
</tr>
<tr>
<td>Measles virus</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>0-40 weeks: increased fetal loss, premature delivery, low birth weight (risks unknown)</td>
</tr>
<tr>
<td>Severe or fatal pneumonia</td>
<td></td>
</tr>
<tr>
<td>Rubella virus</td>
<td></td>
</tr>
<tr>
<td>May be subclinical, especially reinfection</td>
<td>&lt;11 weeks: 90% congenital rubella syndrome</td>
</tr>
<tr>
<td>Clinical rubella with acute symmetrical arthropathy</td>
<td>11-16 weeks: 20% congenital rubella syndrome</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic in up to 50% cases</td>
<td>&lt;20 weeks: 9% excess fetal loss</td>
</tr>
<tr>
<td>Non-specific febrile illness followed by acute symmetrical arthropathy and/or discrete or confluent lacy maculopapular rash</td>
<td>3% develop fetal hydrops with 50% fatality</td>
</tr>
<tr>
<td>Aplastic crisis in sickle cell disease</td>
<td></td>
</tr>
<tr>
<td>Anaemia/pancytopenia in immunocompromised people</td>
<td></td>
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</tbody>
</table>
Table 2 | Diagnosis of index case, timing of transmissibility to susceptible contacts, and incubation periods

<table>
<thead>
<tr>
<th>Viral illness</th>
<th>Type of rash</th>
<th>Diagnosis by NAT</th>
<th>Serological diagnosis in clinical case*</th>
<th>When is it infectious for contacts?</th>
<th>Incubation period (from exposure to rash onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickenpox</td>
<td>Vesicular</td>
<td>Varicella zoster virus DNA in cutaneous lesion</td>
<td>Retrospective diagnosis by IgG seroconversion or IgM detection</td>
<td>48 h before rash onset until lesions are all crusted over VZIG</td>
<td>10-21 days (may be up to 28 days following VZIG)</td>
</tr>
<tr>
<td>Measles</td>
<td>Maculopapular</td>
<td>Measles RNA in oral or throat swab</td>
<td>IgM detectable from day 5 of rash; IgG seroconversion</td>
<td>From 4 days before rash until 4 days after onset of rash</td>
<td>7-18 days</td>
</tr>
<tr>
<td>Rubella</td>
<td>Maculopapular</td>
<td>Rubella RNA in oral or throat swab†</td>
<td>An IgM positive result needs confirmation by seroconversion or IgG avidity‡</td>
<td>From 7 days before rash until 10 days after onset of rash</td>
<td>14-21 days</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Maculopapular</td>
<td>Low level DNA persists for prolonged period in plasma, so detection alone does not confirm recent infection</td>
<td>IgM detectable from rash onset; confirm by positive NAT or IgG seroconversion</td>
<td>From 10 days before onset, ending when rash appears</td>
<td>13-18 days</td>
</tr>
</tbody>
</table>

*Virus specific IgM may no longer be detectable from 4 weeks after the onset of the rash illness.
†Although it is suitable for diagnosis of the index case, NAT testing alone is not sufficiently robust to confirm or exclude clinical rubella in a pregnant woman—this would require specialist interpretation in conjunction with matching serology.
‡Avidity is an estimate of the overall specificity of the serological response. It is used to deduce the timing of the initial maternal infection.
### Table 3 | Evidence of immunity, post-exposure testing, and interventions for mother and fetus or neonate

<table>
<thead>
<tr>
<th>Virus</th>
<th>Satisfactory evidence of immunity following rash exposure in pregnancy</th>
<th>Post-exposure testing to check susceptibility/infection</th>
<th>Post-exposure prophylaxis</th>
<th>Other intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella zoster virus</td>
<td>History of chickenpox (less reliable in tropical/subtropical climates), or 2 doses varicella vaccine</td>
<td>Varicella zoster virus IgG. Consider susceptible if IgG not detected</td>
<td>Prompt VZIG can prevent or attenuate illness in susceptible pregnant women*</td>
<td>Prompt aciclovir therapy for varicella in pregnant woman or neonate.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Short time frame for administration: UK HPA 10 days; USA CDC 4 days</td>
<td>Postnatal maternal varicella vaccination if exposure did not result in infection during pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VZIG for neonate in cases of perinatal maternal varicella</td>
<td></td>
</tr>
<tr>
<td>Measles virus</td>
<td>2 doses measles containing vaccine, or measles IgG-positive test</td>
<td>Measles IgG. Consider susceptible if IgG not detected</td>
<td>HNIG within 6 days of exposure to prevent or attenuate measles in susceptible pregnant woman*</td>
<td>Postnatal maternal MMR or measles vaccination if exposure did not result in infection during pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HNIG for neonate in cases of perinatal maternal measles</td>
<td></td>
</tr>
<tr>
<td>Rubella virus</td>
<td>2 doses rubella containing vaccine, or 2 rubella IgG tests &gt;10 IU/mL, or 1 vaccine and 1 positive IgG test</td>
<td>Rubella IgM and IgG,† Refer if IgM detected. If both negative repeat at least 1 month after most recent exposure</td>
<td>HNIG has been suggested for seronegative pregnant women exposed to rubella for whom termination would be unacceptable, but there is no evidence base</td>
<td>Consider termination if maternal rubella confirmed to have occurred before 16 weeks’ gestation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postnatal maternal MMR or rubella vaccination</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>History unreliable. No vaccine available</td>
<td>Parvovirus IgM and IgG,† Refer if IgM detected. If both negative repeat at least 1 month after most recent exposure</td>
<td>None available</td>
<td>Confirm maternal infection. Monitor for fetal hydrops. Intrauterine transfusion significantly improves outcome in hydrops fetalis</td>
</tr>
</tbody>
</table>

HPA=Health Protection Agency. CDC=Centers for Disease Control and Prevention. HNIG=human normal immunoglobulin.

*In the event of further exposure, another assessment is needed. A second dose of immune globulin may be indicated if more than 3 weeks have elapsed since the first.

†Virus specific IgM tests are subject to false positive results and require careful interpretation, in conjunction with IgG results and IgG avidity if available, on at least two blood samples. Appropriate NAT testing may also be of use.
Viral rash illnesses to consider. Top: vesicular rash—consider varicella zoster. Bottom: maculopapular rash—consider measles, rubella, parvovirus B19