Infections of concern during pregnancy

Prevention and interventions

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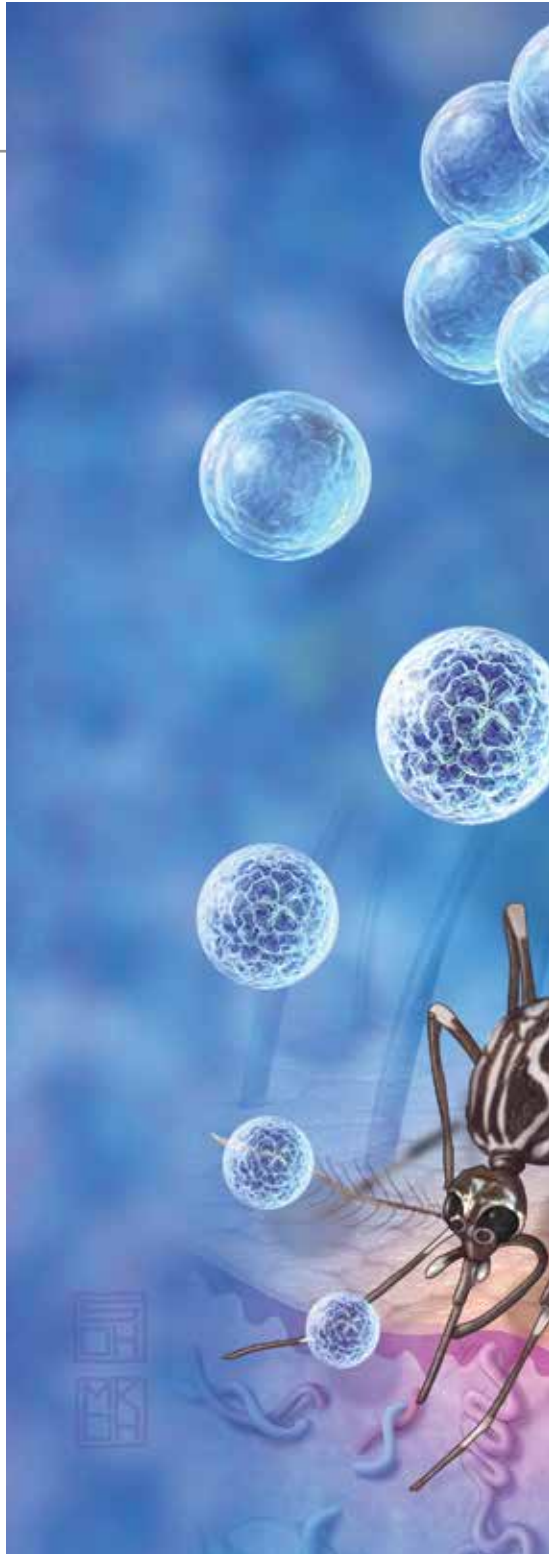
Although a broad range of infections can damage a developing fetus or newborn infant, they do so infrequently and many are preventable. Accurate diagnosis is needed to determine appropriate management.



There is a conventional view that pregnant women are more susceptible to infection because of the pregnancy-associated immunosuppression required to prevent rejection of the fetal 'organ transplant'. In fact, there is little evidence for this. Whereas an organ transplant suddenly exposes the recipient's immune system to foreign antigens, a fetus releases foreign (paternal) antigens in slowly increasing amounts as it develops, inducing tolerance rather than rejection.

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Although there is no significant overall immune suppression in otherwise healthy pregnant women, there is a relative decrease in T-helper (Th) 1 (cell-mediated) immunity and an increase in Th2 (humoral) immunity. In women with borderline immune function, due to malnutrition or HIV infection, these changes may be enough to tip the balance towards increased susceptibility to, or reactivation of, infections that depend on cell-mediated immunity, such as listeriosis or tuberculosis. Latent herpes virus infections (e.g. due to herpes simplex virus [HSV] or cytomegalovirus [CMV]) are more likely to reactivate during pregnancy.

Despite the protective placental barrier, some pathogens, particularly intracellular bacteria and viruses, can breach it and infect the fetus, especially towards the end of pregnancy. However, generally the earlier in pregnancy that fetal infection occurs the greater the risk of damage – from delayed organ growth, abnormal development or inflammatory scarring.

Although infection does not necessarily occur more frequently in pregnant women, illness may be more severe because of anatomical and/or physiological changes that occur in late pregnancy. Reduced lung capacity from upward pressure on the diaphragm increases the risk of pneumonia complicating influenza or varicella infections, and pressure on the ureters increases the risk of pyelonephritis in the presence of bacteriuria.

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KEY POINTS

- Infectious diseases that occur during pregnancy can infect and damage the fetus or neonate, although this happens infrequently.
- Accurate diagnosis of maternal and fetal infections is needed to determine appropriate management.
- Maternal infections are often asymptomatic or cause mild, nonspecific illness; however, some can be more severe due to anatomical and/or physiological changes that occur in late pregnancy.
- Routine antenatal screening is recommended for the presence of, or susceptibility to, a small number of infections for which a safe, effective intervention (i.e. immunisation or treatment) is available, to reduce maternal or fetal/newborn risk.

Infections of greatest concern during pregnancy

The risks of damage to the fetus, newborn infant or child and any adverse effect on pregnancy outcome from maternal infection depend on the pathogen, stage of pregnancy at which infection occurs and whether or not the fetus is infected. Infections most likely to cause significant adverse effects during pregnancy are listed in Tables 1 to 4.[1-3] Many of these infections can be prevented or their effects minimised by appropriate intervention as detailed in the Tables. Even if no treatment is available, timely diagnosis and recognition of serious fetal damage may allow termination of the pregnancy to be considered.

This article discusses infections that are thought to be most commonly seen and therefore of concern in pregnant women and those with associated controversy (such as group B streptococccus [GBS] infection prevention) or uncertainty about appropriate management (CMV infection).

Routine antenatal screening

Many of the infections that are causes of concern during pregnancy are often asymptomatic. Chronic asymptomatic infections due to hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) or syphilis can only be detected by screening, which is performed as part of routine antenatal screening. Susceptibility to rubella or varicella is determined by screening, which is also recommended routinely, preferably before conception so appropriate immunisation can be given.

Routine antenatal screening for various infections is recommended as shown in Tables 1 to 4. It is important that the rationale for screening, how to interpret the results and the appropriate interventions are understood and explained to the patient, to prevent unnecessary anxiety and inappropriate management. It is also important that a system is established to ensure that screening results are reviewed and appropriate action is taken.

Most routine antenatal screening is uncontroversial and universally

TABLE 1. PATHOGENS OF PARTICULAR CONCERN DURING PREGNANCY: TRANSPLACENTALLY TRANSMITTED

Pathogen	Clinical presentation of infection	Fetal/neonatal effects*	Prevention/screening	Intervention
Rubella virus	Exanthem, arthralgia, lymphadenopathy; often asymptomatic	Congenital rubella syndrome; eye, heart, hearing defects*	Routine antenatal screening (IgG)	Postpartum vaccination if seronegative; accurate diagnosis if suspected (IgG seroconversion, IgM); referral
Cytomegalovirus†	Flu-/glandular fever-like illness; lymphadenopathy; mild hepatitis; abnormality on routine ultrasound or screening; usually asymptomatic	Growth retardation; microcephaly; organ calcification; echogenic bowel; hepatosplenomegaly; thrombocytopenia; sensorineural deafness (most common effect); developmental delay; eye defects*	Avoid contact with saliva or urine of infants and toddlers; hand hygiene; reinfection/reactivation of latent infection can cause fetal damage; screening not recommended	Accurate diagnosis if suspected (IgG seroconversion or avidity); referral for amniotic fluid PCR; maternal treatment with hyperimmune CMV immunoglobulin may reduce vertical transmission risk (studies in progress)
Toxoplasma gondii†	Flu-/glandular fever-like illness; lymphadenopathy; usually asymptomatic	Hydrocephalus/ microcephaly; hepatosplenomegaly; chorioretinitis (most common and often only effect)*	Avoid raw or undercooked meat; avoid ingestion of soil (raw vegetables; hand hygiene after gardening)	Accurate diagnosis if suspected (IgG seroconversion or avidity); referral for amniotic fluid PCR; treatment with spiramycin‡ can reduce vertical transmission risk
Treponema pallidum†	Chancre (rare); rash, hepatitis, neurosyphilis etc.; usually asymptomatic	Congenital syphilis: osteitis; rash; meningoncephalitis; hepatosplenomegaly	Routine antenatal screening (Tp Ab; 'regain' test if positive); avoid new sexual partner; practice safe sex	Treat (IV penicillin) if serology reactive; test other children and sexual partner(s); referral
Parvovirus B19	Exanthem, arthralgia; prolonged epidemics; about 50% of young women seronegative[1]	Main risk 9 to 20 weeks' gestation; about 10% fetal loss; hydrops fetalis in about 3% (due to severe anaemia and/ or cardiomyopathy)[1]	Exposure – infection risk if seronegative; occupational, e.g. teachers (20 to 30%); household (50%)[1]	Accurate diagnosis if suspected (IgG seroconversion, IgM); serial ultrasound for hydrops; referral; intrauterine transfusion can reduce fetal loss
Zika virus†	Fever, exanthem; 85% of cases are asymptomatic[2]	Microcephaly (often severe); other CNS abnormalities; arthrogryposis	Avoid travel to endemic area; avoid mosquito bites	Accurate diagnosis by RT-PCR and/or serology; referral

* Severe fetal damage most likely if fetal infection occurs in first trimester; and/or significant fetal/perinatal mortality.
† Usually asymptomatic acute, latent or chronic infection or colonisation.
‡ Spiramycin is not licensed for use in Australia but can be imported by special arrangement from the manufacturer.
Abbreviations: Ab = antibody; CMV = cytomegalovirus; CNS = central nervous system; Ig = immunoglobulin; IV = intravenous; PCR = polymerase chain reaction; RT-PCR = reverse transcriptase polymerase chain reaction; Tp = *Treponema pallidum*.

recommended. However, for some conditions opinions differ about the need for, or method of, screening.

Chlamydia

Chlamydia trachomatis infection is the most common sexually transmitted infection (STI); the notification rate in 2014 in women in Australia was 435.6 per 100,000, predominantly in the 15 to 24 years age group.[4] Chlamydial infection is usually asymptomatic in women but can have serious sequelae, particularly infertility (Table 3). Opportunistic screening is recommended for sexually active women under the age of 30 years, whether pregnant or not, especially if they have had multiple sexual partners in the past 12 months or a previous STI.

The usual screening method for chlamydia is a nucleic acid test (NAT;

TABLE 2. PATHOGENS OF PARTICULAR CONCERN DURING PREGNANCY: TRANSPLACENTALLY AND PERINATALLY TRANSMITTED

Pathogen	Clinical presentation of infection	Fetal/neonatal effects*	Prevention/screening	Intervention
Varicella-zoster virus*	Chicken pox symptoms; symptoms of herpes zoster infection (negligible risk)	Congenital in first or second trimester (<5%) – dermatomal skin scarring, limb deformity, cardiac lesions; postnatal zoster infection; perinatal – life-threatening disseminated infection	Antenatal screening (IgG) if no history of chicken pox or vaccination; urgent serology after exposure if status unknown	If seronegative, zoster immune globulin within 48 to 96 hours of contact; aciclovir for symptomatic infection; postpartum vaccination
Herpes simplex virus†	Flu-like illness; fever (first-degree infection); first-degree or recurrent genital or orofacial lesions; often asymptomatic	Congenital infection rare; perinatal infection – preterm labour; neonatal 'sepsis' and/or mucocutaneous lesions and/or encephalitis*	Avoid new sexual partner; practice safe sex; recurrent genital herpes transmission rare (vaginal delivery)	Accurate diagnosis of suspected (PCR, lesions); treat with aciclovir if symptomatic; screen and/or treat infant if high risk or symptomatic
Human immunodeficiency virus†	Flu-/glandular fever-like illness, rash; usually asymptomatic	About 40% vertical transmission depending on maternal viral load;[3] AIDS if untreated	Routine antenatal screening (HIV Ag/Ab, confirmatory tests if positive); avoid new sexual partner; practice safe sex	If positive, refer; treat with antiretroviral during pregnancy; treat infant after birth; screen/treat sexual partner(s) and other children
Hepatitis B virus†	Acute hepatitis; chronic liver disease; usually asymptomatic	High risk of chronic HBV infection, especially if mother HBeAg positive or has a high viral load	Routine antenatal screening (HBsAg; if positive, HBeAg)	If mother infected, HBIG within 12 hours of birth; HBV vaccine at birth, then two, four and six months
Hepatitis C virus†	Acute hepatitis; chronic liver disease; usually asymptomatic	Low risk of vertical transmission (about 5% – higher if high maternal viral load and/or HIV infection)	Routine antenatal screening commonly performed (HCV antibody plus RT-PCR if positive)	No current intervention if positive; follow mother for possible postpartum treatment; test infant (RT-PCR) at >8 weeks or serology at >18 months

* Severe fetal damage most likely if fetal infection occurs in first trimester; and/or significant fetal/perinatal mortality.
† Usually asymptomatic acute, latent or chronic infection or colonisation.
Abbreviations: Ab = antibody; Ag = antigen; AIDS = acquired immune deficiency syndrome; HBeAg = hepatitis B envelope antigen; HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; RT-PCR = reverse transcriptase polymerase chain reaction.

usually polymerase chain reaction [PCR]) on an endocervical swab, a self-collected vaginal swab or a first-pass urine specimen. It is a simple, sensitive, specific and cost-effective test, and is routinely combined with screening for gonorrhoea (which is a much less common infection).

Treatment of chlamydial infection (with 1 g azithromycin stat) in pregnant women and their sexual partner(s) can prevent neonatal infection (which can cause conjunctivitis and/or pneumonia), postpartum pelvic infection and further transmission. If the initial test is negative, it should be repeated during the third trimester in women at high risk.

Hepatitis C

Routine screening for HCV infection is commonly recommended, although there is currently no way to prevent vertical transmission, which is uncommon (about 5% of infants of women with active HCV infection overall will be infected; Table 2). Potent antiviral agents that can achieve high cure rates have recently become available for all adult patients with HCV, but are not recommended during pregnancy. However, routine antenatal screening can identify infected women allowing for later assessment and treatment of both mother and infant.

If the initial HCV antibody test is positive, reverse transcriptase (RT)-PCR is performed to determine whether infection is active. If it is found to be active, viral load and liver function tests are indicated to assess the risk of vertical transmission and guide future management. The infant

TABLE 3. PATHOGENS OF PARTICULAR CONCERN DURING PREGNANCY: USUALLY PERINATALLY TRANSMITTED

Pathogen	Clinical presentation of infection	Fetal/neonatal effects*	Prevention/screening	Intervention
Group B streptococcus†	Usually asymptomatic; UTI; chorioamnionitis, preterm birth; genital colonisation in 20 to 30% of women	Early-onset neonatal sepsis; meningitis (about one in 2000 births); usually within 24 hours of birth (about 50% onset in utero)	Either: screening culture of vaginal/anal swabs at 35 to 37 weeks Or: clinical 'screen' for risk factors: preterm labour; maternal fever, prolonged rupture of membranes	Intrapartum IV benzyl penicillin prophylaxis for carriers; reduces neonatal colonisation and sepsis rates, but high rate of IV benzyl penicillin with potential adverse effects; IV ampicillin (often pre-emptive treatment) for women with clinical risk factors (especially fever, preterm birth); potential reduction in other types of neonatal sepsis
Escherichia coli†	UTI; chorioamnionitis; diarrhoea	Early-onset neonatal sepsis; pneumonia; meningitis (uncommon, less than one in 2000); stillbirth; prematurity	Routine antenatal screening for AB	Treatment of AB reduces risk of pyelonephritis; IV ampicillin (often pre-emptive treatment) for women with clinical risk factors (especially fever, preterm birth)
Listeria monocytogenes†	Flu-like illness, fever, headache, diarrhoea; sepsis, meningitis (food-borne); often asymptomatic	Early-onset neonatal sepsis, pneumonia, meningitis (rare); fetal death; stillbirth, prematurity	Avoid soft cheeses, cold processed or cooked meat, chicken, pre-prepared vegetables and salads, pre-cut fruit, pate, soft serve ice cream and raw seafood	Confirm diagnosis if suspected (blood culture); treat with penicillin or ampicillin; monitor fetus
Chlamydia trachomatis†	Cervicitis; pelvic inflammatory disease; usually asymptomatic	Neonatal conjunctivitis (1 to 2 weeks); pneumonia (2 to 6 weeks); persistent cough, apnoea, failure to thrive; possible increased risk of preterm birth	Routine antenatal screening (or <25 years and/or at high risk for STIs); NAT on cervical or vaginal swab or urine (usually combined with test for gonorrhoea)	If positive, treat woman and sexual contact(s) with 1 g azithromycin; if negative, repeat near term in high-risk groups

* Severe fetal damage most likely if fetal infection occurs in first trimester; and/or significant fetal/perinatal mortality.
† Usually asymptomatic acute, latent or chronic infection or colonisation.
Abbreviations: AB = asymptomatic bacteriuria; IV = intravenous; NAT = nucleic acid test; STI = sexually transmitted infection; UTI = urinary tract infection.

should be tested by RT-PCR at three months of age or later. HCV antibody tests are unreliable before about 18 months, because the presence of maternal antibodies can give a false-positive result.

GBS colonisation and infection

Intrapartum antibiotic prophylaxis (with intravenous [IV] benzyl penicillin) for women with anovaginal GBS colonisation can reduce early-onset neonatal GBS colonisation and infection by about 80 to 90%.[5]

Routine antenatal screening for GBS carriage is widely, but not universally, recommended at 35 to 37 weeks' gestation (Table 3).[6] This screening is controversial because:

- GBS carriage is common (detectable in 20 to 30% of healthy women depending on methods used) and often intermittent
- early-onset neonatal GBS sepsis is uncommon (about 0.5 per 1000 live births)
- the predictive value of antenatal screening for maternal carriage at delivery and, especially, for neonatal sepsis is low
- based on screening, a high proportion of healthy women will be given IV benzyl penicillin during a normal vaginal delivery with

TABLE 4. PATHOGENS OF PARTICULAR CONCERN DURING PREGNANCY: MATERNAL INFECTIONS

Pathogen	Clinical presentation of infection	Fetal/neonatal effects*	Prevention/screening	Intervention
Influenza virus	Fever, cough, sore throat, headache, myalgia; increased risk of pneumonia, ICU admission, death; exacerbated by obesity, diabetes, asthma, smoking	Prematurity; fetal death/ stillbirth; growth restriction; CNS damage associated (cerebral palsy) with maternal fever	Influenza vaccination for all women, especially those who will be in the second or third trimester during influenza season	Confirm diagnosis if suspected (point-of-care test; PCR if negative, but do not wait for result); start treatment with oseltamivir as soon as possible after onset of symptoms (within 48 hours if possible); consider prophylaxis within 48 hours of known close contact
Sepsis-causing bacteria	Fever, rigors, local pain, tachycardia, shock; third trimester/postpartum; chorioamnionitis/UTI	Prematurity; fetal death/ stillbirth; CNS damage (cerebral palsy) associated with maternal fever; neonatal sepsis	Routine screening for asymptomatic bacteriuria; treat if positive; causes include *Escherichia coli*, GBS, anaerobes, group A streptococcus, *Staphylococcus aureus, Enterococcus* etc.	If suspected, collect two sets of blood cultures; start empiric therapy stat – IV ampicillin, gentamicin, metronidazole; review when cause known
Bordetella pertussis	Persistent cough; modified pertussis if previously immunised	Neonatal pertussis before immunisation - high mortality	Maternal immunisation (dTpa) during third trimester	Diagnosis by PCR on throat swab or serum pertussis IgA. Treatment or postexposure prophylaxis with e.g. azithromycin (500 mg on day 1, followed by 250 mg/day on days 2 to 5).

* Severe fetal damage most likely if fetal infection occurs in first trimester; and/or significant fetal/perinatal mortality.
† Usually asymptomatic acute, latent or chronic infection or colonisation.
Abbreviations: CNS = central nervous system; GBS = group B streptococcus; ICU = intensive care unit; Ig = immunoglobulin; IV = intravenous; PCR = polymerase chain reaction; UTI = urinary tract infection.

potentially serious, although rare, adverse effects, such as maternal anaphylaxis and interference with establishment of the normal infant microbiome.

An alternative approach to the prevention of neonatal GBS and potentially other causes of sepsis is to treat women with clinical 'risk factors' or possible markers of intrauterine infection (i.e. unexplained preterm labour at less than 37 weeks' gestation, fever above 38°C and/or prolonged rupture of membranes taking more than 18 hours) with IV benzyl penicillin or ampicillin during labour. Giving antibiotics in this situation can be seen as pre-emptive therapy for maternal and/or congenital sepsis. Although only 60 to 70% of mothers of infants who develop early-onset GBS sepsis have any of these risk factors, this approach restricts the use of IV benzyl penicillin to a high-risk group. A recent review of early-onset GBS infections suggests that risk factors or known carriage are often overlooked, and screening can be falsely negative.[7]

Immunisation during pregnancy

Immunisation, if available, is the safest and most reliable way to prevent maternal or fetal infection.[8] Most young women will have been fully immunised during childhood and adolescence, but this should be opportunistically checked in young women of childbearing age, particularly immigrants or refugees, who present to a GP for any reason.

In general, inactivated or subunit vaccines can be given safely during pregnancy but live-attenuated vaccines (such as the measles, mumps, rubella, varicella [MMRV] vaccine) are contraindicated. However, there is no evidence of fetal damage resulting from inadvertent administration, even in the first trimester.

Vaccines routinely recommended during pregnancy are:

- annual influenza vaccine, given at any stage of pregnancy and is especially important for those women who will be in their second or third trimester during the influenza season
- adult diphtheria, tetanus, acellular pertussis (dTpa) vaccine.

Influenza in the second or especially the third trimester is more likely to be

severe and to require hospital and ICU admission of the women compared with influenza in otherwise similar non-pregnant women.[9] The mortality from pneumonia is increased, especially during pandemics and in women with comorbidities, such as obesity, asthma or diabetes, or who are smokers.

Neonatal tetanus is virtually unheard of in western countries. However, it is an important cause of infant mortality in many developing countries in the absence of routine tetanus immunisation.

The protective effect of the acellular pertussis vaccine, even after a full course, wanes over time. The duration of protection is highly variable, depending on factors such as age, previous exposure to pertussis infection and number of vaccine doses received. Infection in previously immune individuals is usually mild but can be a source of transmission to others. Young infants who have not yet been fully immunised are at risk from severe pertussis, even if acquired from a fully immunised person with mild or atypical disease. Booster immunisation of the mother during the third trimester provides significant protection to the infant during this vulnerable period.

Presentation of infection during pregnancy

Influenza-like or glandular fever-like illnesses

The differential diagnoses of nonspecific acute febrile illness are broad and include some conditions that have potentially serious fetal effects, even if maternal symptoms are mild or transient, such as CMV infection, toxoplasmosis, *Listeria monocytogenes* infection, secondary syphilis or influenza. Rarely, primary HSV or HIV infections can present as a nonspecific febrile illness without distinguishing features.

Depending on the patient's history and the presence of other symptoms and signs (e.g. cough, sore throat, vomiting, diarrhoea, headache, hepatosplenomegaly, lymphadenopathy), investigations may include:

- full blood count
- liver function tests
- blood culture
- serology for CMV IgG and IgM
- serology for *T. gondii* IgG and IgM
- serology for HIV antigen/antibody (repeat serology, if negative, in 10 to 14 days)
- NAT or culture of any genital or orofacial lesions for HSV
- point-of-care test (POCT) on nose/throat swabs for influenza and PCR for respiratory viruses (including influenza virus).

Cytomegalovirus infection

Congenital CMV infection is the most common cause of nonhereditary sensorineural deafness and congenital, mainly neurodevelopmental, abnormalities.[10] About 50% of women of childbearing age are susceptible to primary CMV infection and on average 1 to 2% will be infected, usually asymptomatically, each year.[11] Viral replication is rapidly controlled by the normal host immune response but the virus remains in latent form in the body for life. Reinfection or reactivation can occur in CMV-seropositive women (i.e. with latent infection). There is currently no vaccine or proven therapy to prevent symptomatic congenital CMV infection.

The most common source of primary CMV infection or reinfection in young women is intimate contact with young children, especially toddlers attending day care centres where CMV is often spread from one person to another. Infected infants and toddlers can excrete CMV in their saliva and urine for months. There is a high seroconversion rate among CMV-seronegative women in the months after their children begin attending day care and among day care centre staff.

Ideally, all women should have a CMV IgG test before they become pregnant. Whether or not their immune status is known, pregnant women should take precautions to avoid direct contact with the saliva or urine of young infants, which can be difficult for mothers of toddlers (Table 1). A sexual partner is also a potential, but less likely, source of CMV infection.

If symptoms that are consistent with primary CMV infection occur, CMV serology should be performed as soon as possible and repeated, if negative, 10 to 14 days later. Seroconversion or a significant increase in IgG levels are the best evidence of a primary CMV infection; the presence of CMV IgM suggests but does not prove recent infection. High IgG avidity suggests past infection, more than three months ago; low IgG avidity, suggests more recent infection.

If primary maternal infection is confirmed or strongly suspected during the first trimester, CMV PCR and/or culture on amniotic fluid can detect fetal infection. However, amniocentesis should be delayed until at least six weeks after maternal infection or seroconversion or 20 to 21 weeks' gestation. Severe fetal damage during early pregnancy can often be detected by routine ultrasound examination.

There is no proven intervention to prevent fetal infection, and reinfection or reactivation can also cause fetal damage, albeit less frequently and usually less severely than primary infection. Randomised controlled trials of hyperimmune CMV globulin have shown promising, but inconclusive, results.[12] Until the results of ongoing studies are known, routine antenatal screening is not recommended.

Toxoplasmosis

Toxoplasmosis is caused by the protozoan parasite *T. gondii*, of which the definitive hosts are members of the cat family.[10] Oocysts excreted in the faeces of infected cats are infective after several days in the environment if ingested by warm-blooded animals, including humans. Food-producing animals that feed on contaminated pasture become infected when

oocysts penetrate the gut wall and spread to muscle and brain, where they form tissue cysts that are infective when ingested. Human infection most commonly occurs when eating infected, undercooked meat or, less commonly, by inadvertently ingesting contaminated soil, such as when gardening or eating inadequately washed raw vegetables. Direct contact with cats is rarely implicated.

Acute toxoplasmosis is uncommon in Australia. Infection is usually asymptomatic or causes a mild illness, often associated with lymphadenopathy (Table 1). Severe congenital toxoplasmosis (i.e. chorioretinitis, hydrocephalus, multisystem disease) is rare, but varying combinations of less severe sequelae (usually chorioretinitis) can result from intrauterine infection.

Routine antenatal screening is not recommended. If maternal toxoplasmosis is suspected, because of a compatible illness, the diagnosis can be made by detection of seroconversion or a significant increase in IgG levels. Interpretations of toxoplasma IgM and IgG avidity are similar to those for CMV.

If acute maternal toxoplasmosis is confirmed, treatment with spiramycin can reduce the risk of fetal infection and damage. This macrolide antibiotic is not licensed for use in Australia but can be imported by special arrangement with the manufacturer. Its use should be supervised by a specialist in infectious diseases in pregnancy. The likelihood of fetal infection increases from less than 10% when maternal infection occurs in the first trimester, to about 40% in the second trimester and about 70% in the third trimester.[13] The risk of significant sequelae is high at about 60% in the first trimester, and decreases to 25% and less than 10% in the second and third trimesters, respectively.[13] Fetal infection can be detected by PCR examination of amniotic fluid collected six weeks or more after maternal infection or at more than 20 weeks' gestation. Severe fetal damage can often be detected by ultrasound examination.

Listeriosis

Listeriosis is an uncommon food-borne infection caused by the Gram-positive bacterium *L. monocytogenes*. Infection is often asymptomatic or causes vomiting and diarrhoea or a nonspecific febrile illness with headache and myalgia (Table 3). It is usually self-limiting, except in frail elderly people in whom it can cause life-threatening sepsis. However, when it occurs during pregnancy, either with or without symptoms, it can cause fetal death, stillbirth, preterm delivery, congenital/neonatal sepsis and/or meningitis.

If listeriosis is suspected, the diagnosis can be confirmed by blood culture. If symptoms of sepsis are present, treatment should be started immediately with IV ampicillin, gentamicin and metronidazole (empirical therapy for sepsis) until culture results are known.

Influenza

If influenza is suspected during pregnancy, nose and throat swabs should be collected for a POCT, if available (Table 4). Testing kits are available for GPs or pathology laboratories have them available for rapid screening. If the test is positive, treatment with 75 mg oseltamivir, 12-hourly for five days, should be given. If started within 48 hours of the onset of symptoms, oseltamivir can significantly reduce the risk of severe illness and the need for hospital admission in pregnant women. If the POCT is negative, but the diagnosis is strongly suspected, PCR for influenza and other respiratory viruses is indicated.

Febrile illness with rash

Many acute viral exanthemata can occur in susceptible pregnant women, particularly if the women are exposed to young children at home or in the workplace. Previously, the greatest concern was rubella, which is now uncommon. Maternal infection with parvovirus and the mosquito-borne Zika virus, among others, can also cause serious but very different fetal diseases.

Rubella

Rubella is usually a trivial, self-limiting illness, which was once common in children and young adults, causing mild fever, rash, occipital lymphadenopathy and, particularly in adult women, small joint arthralgia (Table 1). Congenital rubella syndrome (CRS) was first recognised in 1941 when the Sydney ophthalmologist Norman Gregg noted a sudden increase in the number of babies presenting with unusual, bilateral, congenital cataracts, suggesting a common cause early in fetal development. His enquiries showed that many of these infants' mothers had had 'German measles' (rubella) in the first trimester of pregnancy.[15]

Between 2004 and 2013, there were only five cases of CRS in Australia and all five mothers were born overseas.[16] Country of birth, especially Asia, is the strongest predictor of rubella susceptibility among pregnant women. Routine antenatal screening for rubella IgG and postpartum immunisation of seronegative women should continue indefinitely.

Parvovirus B19 infection

Parvovirus B19 causes prolonged epidemics of erythema infectiosum (also known as 'fifth disease' or 'slapped cheek syndrome'), particularly in primary school-aged children (Table 1). Apart from the typical 'lacy' rash, such as that seen in cases of rubella, it often causes small joint arthralgia in adult women. Otherwise it is benign, self-limiting and often asymptomatic. The virus causes maturation arrest of red cell precursors, resulting in acute anaemia, which is usually transient and subclinical. However, it is a potentially serious infection in individuals with high red cell turnover, including people with sickle cell anaemia (in whom it causes aplastic crisis) and fetuses.

About 40% of women of childbearing age are susceptible to infection with parvovirus B19, and annual seroconversion rates vary from 1.5% during endemic periods to between 10 and 15% during epidemics.[1] Infection occurs in about

20 to 30% of susceptible women following occupational exposure (e.g. primary school teachers) and in 50% of those exposed at home.[1]

Maternal infection in the first half of pregnancy is associated with excess fetal loss in 10% of cases and hydrops fetalis due to severe anaemia in 3% of cases.[1] No long-term sequelae or congenital abnormalities have been attributed to parvovirus B19 infection. The overall risk of serious adverse outcome from exposure to parvovirus B19 infection during pregnancy is low, irrespective of maternal symptoms (excess early fetal loss occurs in two to six per 1000 pregnancies and fetal death from hydrops fetalis occurs in two to five per 10,000 pregnancies).[1]

Hydrops fetalis can occur suddenly, usually five to eight weeks after maternal infection; it can cause fetal death (in about one-third of cases) or resolve spontaneously or after specialised treatment (intrauterine blood transfusion). If suspected, the diagnosis should be confirmed by maternal serology (IgG seroconversion and/or parvovirus IgM) so that if hydrops does occur then it can be detected as early as possible by serial ultrasound examination.

A small proportion of cases of hydrops (5 to 14%) detected on routine ultrasound examination in the absence of a history of maternal parvovirus will be due to parvovirus B19. However, it will likely be too late to demonstrate seroconversion of IgM (IgG will be present, but levels remain stationary). The diagnosis of fetal infection can be made by PCR of amniotic fluid.

Zika virus infection

Zika virus is an arbovirus and is spread by *Aedes* species mosquitoes (particularly *Aedes aegypti*). It has been recognised as a cause of human infection for more than 40 years but was generally regarded as insignificant because only a minority (about 15%) of people infected, mainly in Africa and southeast Asia, developed a mild dengue-like illness (Table 1). It first came to notice in 2007 and 2013–14 when it caused widespread outbreaks among naïve populations in the Yap Islands (Micronesia) and French Polynesia, respectively.

Serious adverse outcomes of infection were not recognised until October 2015, when an increase in the number of cases of severe microcephaly were reported in north-eastern Brazil, about six months after the onset of a very large epidemic, which started in March 2015 and now involves most of South and Central America. At this stage it is not known whether the association of Zika virus and microcephaly is novel and due to a mutated form of the virus or whether microcephaly was not previously noticed because the affected countries did not routinely record its occurrence and/or the occurrence was not as large as in Brazil.

In the 12 to 15 months since the start of the epidemic, epidemiological and virological evidence has been accumulating that implicates Zika virus as a cause of microcephaly and other central nervous system abnormalities in fetuses.[16] The greatest risk is from maternal infection in the first trimester when, based on limited information, fetal infection probably occurs in 1 to 10% of cases.[17] Intensive research is under way to define the risks and develop improved methods of mosquito control, a vaccine and other preventive strategies.

A. aegypti are found in Far North Queensland, where mosquito control measures have been in place for many years to manage the risk of imported dengue fever. Zika virus infection is unlikely to be acquired in Australia, but can present in recently returned travellers from areas where it is currently circulating, including many Pacific Islands and countries in South and Central America.

Further information and guidelines for the prevention, diagnosis and management of Zika virus are available from the Australian Government Department of Health.[2]

Conclusions

Infectious diseases often cause great anxiety, especially when they occur during pregnancy or in large outbreaks. Although many pathogens can be vertically transmitted from infected or colonised pregnant women, there are several safe, cost-effective interventions that, if implemented routinely, can supplement the robust, natural, physical and immunological defences that normally protect the fetus and infant. However, there are exceptions – such as CMV and GBS infections – for which vaccines and/or safe effective therapies are needed. New threats, such as Zika virus, are likely to be recognised or emerge in the future. MT

Further reading

Palasanthiran P, Starr M, Jones C, Giles M, eds. Management of perinatal infections. Sydney: Australasian Society for Infectious Diseases; 2014. Available online at: https://www.asid.net.au/documents/item/368 (accessed July 2016).

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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Infections of concern during pregnancy

Prevention and interventions

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References

1. Gilbert GL. Parvovirus B19 infection and its significance in pregnancy. Commun Dis Intell 2000; 24 Suppl: 69-71.
2. Australian Government Department of Health. Zika virus – information for clinicians and public health practitioners. Canberra: Department of Health; 2016. Available online at: http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-zika-health-practitioners.htm (accessed July 2016).
3. Newall M-L. Prevention of mother-to-child transmission of HIV: challenges for the current decade. Bulletin of the World Health Organization 2001; 79: 1138-1144.
4. The Kirby Insititute. 2015 Annual Surveillance Report of HIV, viral hepatitis, STIs (Figures 103, 106). Sydney: The Kirby Institute; 2015. Available online at: https://kirby.unsw.edu.au/content/2015-asr-figures-data (accessed July 2016).
5. Lin F-YC, Weisman LE, Azimi P, et al. Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B streptococcal disease. Pediatr Infect Dis J 2011; 30: 759-763.
6. Homer CS, Scarf V, Catling C, Davis D. Culture-based versus risk-based screening for the prevention of group B streptococcal disease in newborns: a review of national guidelines. Women Birth 2014; 27: 46-51.
7. Ko DW, Zurynski Y, Gilbert GL; GBS Study Group. Group B streptococcal disease and genotypes in Australian infants. J Paediatr Child Health 2015; 51: 808-814.
8. Lindsey B, Kampmann B, Jones C. Maternal immunization as a strategy to decrease susceptibility to infection in newborn infants. Curr Opin Infect Dis 2013; 26: 248-253.
9. Duryea EL, Sheffield JS. Influenza. Threat to maternal health. Obstet Gynecol Clin N Am 2015; 42: 355-362.
10. Ville Y, Leruez-Ville M. Managing infections in pregnancy. Curr Opin Infect Dis 2014; 27: 251-257.
11. Seale H, McIntyre CR, Gidding HF, et al. National serosurvey of cytomegalovirus in Australia. Clin Vaccine Immunol 2006; 13: 1181-1184.
12. Revello MG, Lazarotto T, Guerra B, et al. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus N Engl J Med 2014; 370: 1316-1326.
13. Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. Lancet 1999; 353: 1829-1833.
14. Gregg, NM. Congenital cataract following German measles in the mother. 1941. Epidemiol Infect 1991; 107: iii-xiv.
15. Khandaker G, Zurynski Y, Jones C. Surveillance for congenital rubella in Australia since 1993: cases reported between 2004 and 2013. Vaccine 2014; 32: 6746-6751.
16. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects - reviewing the evidence for causality. N Engl J Med 2016; 374: 1981-1987.
17. Johansson MA, Mier-Y-Teran-Romero L, Reefhuis J, Gilboa SM, Hills SL. Zika and the risk of microcephaly. N Engl J Med 2016 [Epub ahead of print].