Infectious disease in pregnancy

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Abstract

Most infections during pregnancy will not cause long-term harm, but those that do should be recognized and treated in conjunction with infectious diseases specialists and neonatologists where appropriate. Mothers may die from obstetric sepsis, more commonly in the developing world, and some infections, notably influenza and varicella, run a more severe course in pregnancy. Importantly, despite an overall reduction in the number of maternal deaths in the last UK confidential enquiry, the number of women dying from infection has increased. Maternal infection can also lead to fetal congenital anomalies, stillbirth, preterm deliveries, intrauterine growth restriction and neonatal infection. This review outlines prevention and screening for infections, maternal infection syndromes, important organisms with their clinical effects and management in pregnancy, and those infections that may lead to congenital abnormalities.

Keywords congenital anomalies; congenital infections; H1N1 influenza; maternal mortality; neonatal infections; vertical transmissions

Introduction

All infectious diseases can occur in pregnant women. There are some that occur more frequently in this group due to the immunosuppressive nature of pregnancy. There are others that cause increased concern in pregnancy due to their potential fetal complications. In this article we will focus on some of the general principles for management of any infection in pregnant women and then discuss some of the diseases in more detail.

Physiological changes

Physiological and immune changes occur in pregnancy making women more susceptible to infections, and these are still not fully understood. A shift from cell-mediated to humoral immunity occurs, which may affect susceptibility to and severity of some infectious diseases, including an increased incidence of certain intracellular pathogens, such as toxoplasmosis, listeriosis, influenza and varicella.

Urinary tract infections are more common, related to progesterone effects and mechanical compression by the gravid uterus, as well as higher urinary glucose and pH facilitating bacterial growth.

Respiratory infections may be more severe for several reasons. Diaphragmatic elevation reduces secretion clearance and functional residual capacity, and with the increased oxygen demand, reduces tolerance to hypoxia, particularly in the third trimester. Gastric acid aspiration is more common, and increased interstitial lung water is seen, increasing the risk of acute lung injury.

Antenatal screening and prevention

Screening

Since 2003, the UK Department of Health has recommended screening for hepatitis B, HIV, rubella and syphilis early in pregnancy with a single blood sample, as well as asymptomatic bacteriuria (ASB) with a urine sample. There is currently no clear evidence of benefit from screening for other infections, although women may request additional screening, particularly if they have experience of healthcare systems overseas. Whilst the current guidance in the UK is not to screen women for group B streptococcus (GBS), cytomegalovirus (CMV) and toxoplasmosis, each case should be considered on an individual basis and consultation with local infectious diseases/virology services may be required. For women at high-risk for HIV it is important to repeat the HIV test in the third trimester. A negative test at booking can be falsely reassuring and seroconversion during pregnancy carries a higher risk of mother to child transmission.

Primary prevention

Mothers are advised about primary prevention measures to avoid toxoplasmosis infection such as thorough hand washing, cooking raw meats, and avoiding contact with cat litter and soil. Listeria avoidance includes not eating unpasteurized dairy products or pate and washing salads thoroughly.

Immunization

Ideally women should be immunized prior to conception, but there are a few situations where immunization of a pregnant woman is indicated. Live vaccines are usually avoided though, due to the risk of fetal infection.

UK immunization programs for rubella in childhood should protect during childbearing years. The single vaccine has been in place since 1970, and the MMR since 1988. Until recently, the UK childhood immunization rates were 92%. Following the 2003 negative press coverage, rates dropped to 80%, although they have started to increase again. Women planning a family should ensure immunity.

Live Varicella vaccines are available pre-pregnancy, and zoster immune globulin should be given to pregnant women non-immune to varicella and up to 10 days following exposure. Varicella serology is also available, although immunity is usually assumed from the history of typical rash.

Influenza vaccination (inactivated) may be considered and is deemed safe throughout pregnancy. In light of the recent outbreak of H5N1 influenza and its increased severity in pregnant women, all women should be offered the seasonal vaccine which will give protection to the most common circulating strains.

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Investigation and management

Principles

A good history is essential, considering the pregnancy, gestational age, prior asymptomatic bacteriuria, sexually transmitted infections (STIs), travel, occupation, HIV risk factors, contacts with infectious diseases, and prior tuberculosis (TB) infection. There may only be non-specific symptoms and signs, but these are important to consider, as obstetric sepsis can present this way before rapid deterioration.

Involvement of the feto-maternal multidisciplinary team is essential, including clinical microbiologists/virologists/infectious diseases, local TB services and the critical care team when appropriate. With evidence of STIs, genitourinary physicians should be involved, and screening for other STIs should be undertaken.

Antibiotic use in pregnancy

In general, penicillins, cephalosporins, and macrolides such as erythromycin (although less data on clarithromycin) are safe. Clindamycin is also probably safe although clinical experience is limited. Penicillins are only 50% protein-bound and can cross the placenta to achieve fetal concentrations that are therefore 50% of maternal levels. Amoxicillin has increased renal clearance in pregnancy therefore theoretically higher doses are needed, although in clinical practice, doses are used as outside pregnancy. Augmentin was shown to increase the risk of neonatal necrotizing enterocolitis in one study of preterm premature rupture of membranes prevention, and although no animal studies have shown harm, further human studies are needed. Cephalosporins cross the placenta less commonly and appear to have no adverse fetal effects.

Other antibiotics are relatively contraindicated in pregnancy, but their use may be appropriate depending on the clinical situation. Nitrofurantoin is generally considered safe, but should be avoided at term because of the risk of haemolytic anaemia in the neonate. There are reports of ciprofloxacin causing an arthropathy in animal studies but no adverse human effects have been reported. Trimethoprim has also caused adverse effects in animals, so should be used with caution in pregnancy, especially as it may interfere with folic acid metabolism. It should be avoided near term when used as co-trimoxazole (septrin) in combination with a sulfonamide, as the later can cause fetal kernicterus. Tetracyclines increase the risk of fulminant maternal hepatitis in the third trimester and may stain fetal teeth after 20 weeks gestation. Chloramphenicol should be used with caution because of the association with the 'grey baby syndrome' (characterized by cyanosis, flaccidity and cardiovascular collapse) when used in newborn infants. Aminoglycoside use (e.g. gentamicin) risks fetal ototoxicity and should only be used if there is evidence of serious gram-negative infection. Similarly, vancomycin has been associated with fetal nephrotoxicity and ototoxicity.

Maternal infection syndromes

Sepsis

Obstetric sepsis is the most important cause of UK maternal mortality: in the most recent confidential enquiry, the mortality related to sepsis increased from 0.85 deaths per 100,000 mortalities in 2003–2005 to 1.13 deaths in 2006–2008, making sepsis the most common cause of direct maternal death. The commonest source is the genital tract, notably from *Streptococcus pyogenes* (group A streptococcus, GAS), although it is important to remember that any systemic infections can present as sepsis or septic shock.

Sepsis can present at any time before, during or following delivery and is important to recognize and treat early, for example using early warning score systems for ward patients, and with community midwives being astute for signs of infection. Mothers often present with vague symptoms and signs, but it is important to recognize these early, as the course can be fulminant. Management of septic shock is similar to that outside pregnancy. Preventative measures include good perineal hygiene.

Most obstetric sepsis occurs post-partum, and may relate to genital tract infections, mastitis, thrombophlebitis, episiotomy and perineal tear infections, Caesarean section (CS) wound infections, gastric acid aspiration or post-general anaesthesia pneumonia.

Antepartum infections include chorioamnionitis which may follow prolonged premature rupture of membranes (pPROM) and prolonged labour. PPROM complicates only 2% of pregnancies but is associated with 40% of preterm deliveries, and is suspected with a suggestive maternal history and on a sterile speculum examination. Mothers should be observed 12-hourly for signs of clinical chorioamnionitis. First line prophylaxis for pPROM is erythromycin. Diagnosis of chorioamnionitis is suggested by fever late in pregnancy, uterine tenderness, offensive vaginal discharge and fetal tachycardia. Consequences include PROM and premature labour, increased risk of neonatal pneumonia, bacteraemia, meningitis and death. Treatment is with broad-spectrum antibiotics (ampicillin and gentamicin) and delivery.

Endometritis is a spectrum of endometrial, myometrial and parametrial infections, all of which can be serious, especially when associated with GAS and *Streptococcus agalatiae* (GBS). GAS necrotizing fasciitis and toxic shock syndrome can occur unexpectantly following an uncomplicated pregnancy and delivery, and management includes antibiotic therapy with broad-spectrum antimicrobials according to local policy and early surgical intervention. 30% of the fevers seen in women who have just delivered are due to endometrial infection. The risk is higher post CS and after a PROM, prolonged delivery or in the presence of retained products of conception. Infections are often polymicrobial, with aerobes and anaerobes, and Chlamydia can cause late endometritis. Endometritis can also result from CS wound incisions (more commonly seen following emergency CS), which is important to recognize, as utero-cutaneous fistulae may result requiring surgery. Late endometritis more typically follows vaginal delivery. A 2002 Cochrane review concluded that a single dose of ampicillin or first-generation cephalosporins was sufficient to reduce puerperal infections related to uncomplicated CS, given as a single dose after cord clamping.

For an excellent summary of sepsis see chapter 16 of the recent 2006–2008 confidential enquiry into maternal deaths.

Urinary tract infections

Urinary tract infections (UTIs) are divided according to the site of bacterial proliferation into asymptomatic bacteriuria (ASB), cystitis, and pyelonephritis.

ASB is defined as urine colonization greater than 10^5 CFU/mL on two consecutive clean-catch urine samples (without nitrites or leucocytes on dipstick). It occurs in 4–7% of pregnant women, and is important to recognize, as symptomatic UTIs develop in 20–40% of cases, and there is an increased incidence of preterm delivery and low birth weight infants. This has lead to UK screening being recommended (see NICE guidelines). ASB is due to *Escherichia coli* in 75–90% of cases, and cephalosporins are more appropriate than amoxicillin, given the 60% *E. coli* beta-lactam resistance seen. Up to 15% will require a further course later in pregnancy.

Cystitis or bladder infection occurs in 1–4% of pregnancies, and pyelonephritis, where the kidney is the focus in 2% of all pregnancies.

Pyelonephritis is a serious medical condition in pregnancy, associated with fetal and maternal morbidity, and leads to an increased risk of premature labour. Two-thirds of cases present in the second or third trimester, and 27% post-partum. The right kidney is most often affected due to dextro-rotation of the uterus. The common presenting features are fever, loin pain, rigors, and less often with symptoms of cystitis. Pyelonephritis is the most common cause of septic shock in pregnancy, and adult respiratory distress syndrome (ARDS) occurs in 1–8% of cases, so patients should be closely monitored. Diagnosis is based on the presence of significant bacteriuria following mid-stream urine (MSU) culture, and the history and clinical signs. A renal tract ultrasound scan should be performed to exclude hydronephrosis and structural abnormalities. Organisms are similar to those in lower tract UTIs, with *E. coli* in 70–80%, and *Klebsiella pneumoniae* and *Proteus* species less commonly, but important in recurrent cases. Antibiotic choice reflects local guidelines, usually with a first-generation cephalosporin, or combination ampicillin with gentamicin. Most will be afebrile and asymptomatic following 48 h of appropriate antibiotic treatment and intravenous therapy is then continued until the patient has been afebrile for 48 h. Failure to respond after the initial 72 h usually indicates a resistant organism, renal tract stone or anatomical obstruction. When discharged home, the mother should be more closely watched for recurrence with monthly urine cultures. Fetal effects of untreated pyelonephritis include preterm delivery and low birth weight. If GBS is detected in maternal urine, it should be treated and appropriate intra-partum prophylaxis administered (see later).

Cranberry juice has been used traditionally to prevent and treat UTIs. It contains proanthocyanidins which prevent the adherence of bacterial pathogens to uroepithelium. A recent Cochrane review showed a significant reduction in UTIs compared with placebo, although this was not specific to pregnancy.

Respiratory tract infections

Bacterial pneumonia has a similar incidence and outcome in pregnancy, although viral pneumonias are more common and run a more severe course in pregnancy. Investigation and management are similar, although delay in obtaining a chest X-ray (CXR) is common: remember that the radiation exposure is only 0.05% that of the max recommended 0.2 rad. Influenza and varicella pneumonia in pregnant women have historically been associated with a higher rate of morbidity and mortality. Some important pathogens are considered below, and others, including tuberculosis, in later sections.

Respiratory pathogens in pregnancy:

Upper respiratory tract infection (URTI) – pregnant women often find they have a persistent cold in the last trimester. Whilst this may be due to any of the common viral pathogens such as rhinovirus, there is no treatment and in the absence of lower respiratory tract symptoms does not need investigation.

Bacterial pneumonia – the most common cause of pneumonia in pregnant women remains the same as in the general population – *Streptococcus pneumoniae*. This is usually fully sensitive to amoxicillin (with some decreased susceptibility in strains from abroad).

Influenza pneumonia – influenza infection presents with similar self-limiting symptoms, but if they last more than 5 days complications are not unusual. Pneumonia has a greater mortality rate (up to 50%) in pregnancy, and may result from a secondary bacterial pneumonia (*Staphylococcus aureus*, *Pneumococcus*, or *Haemophilus influenzae*) or viral parenchymal infection.

Complications from pandemic influenza A (H1N1) are more common in pregnancy, notably severe ARDS. Treatment is with the neuraminidase inhibitor oseltamivir (Tamiflu), which should be started as soon as possible until clinical improvement occurs, although data are limited in pregnancy. See WHO guidelines for further details. In cases that remain hypoxic despite maximal invasive mechanical ventilation, veno-venous extracorporeal membrane oxygenation (ECMO) may be required. This is a form of 'lung bypass' to rest the lungs while they recover, and successful cases have been reported during pregnancy and immediately post-partum.

Varicella pneumonia – primary varicella infections are more severe in pregnancy, and progression to varicella pneumonia is more common (10–20% of those infected). Maternal mortality from varicella pneumonia is higher in pregnancy (35% versus 11%), thus prevention of primary infections is of great importance. Oral mucosal ulceration is common, and respiratory illness ranges from coryzal symptoms to severe respiratory failure requiring mechanical ventilation. Classically, the CXR shows bilateral miliary nodular shadowing, and later pulmonary calcification.

Other causes of pneumonia – *Pneumocystis jiroveci* pneumonia (PCP, previously called *P. carinii* pneumonia) in HIV-positive patients is associated with adverse obstetric outcome, and should be treated with co-trimoxazole. PCP is also increasingly being seen in immunocompetent hosts, previously only associated with immunodeficiency. One study showed that asymptomatic nasal carriage of *P. jiroveci* is more common in pregnancy, and another that PCP is more severe in pregnancy. In HIV-positive women, *P. jiroveci* may be transmitted perinatally.

Chlamydia psittaci is an unusual cause of atypical pneumonia, (i.e. those organisms not causing a 'typical' lobar pneumonia). It is usually transmitted via infected birds, may cause a severe illness during pregnancy, but recovery is usually full.

Fungal pneumonia, although unusual, may also run a more severe course in pregnancy, especially in the final trimester.

Hepatitis

Viruses causing hepatitis include the hepatitis viruses A–E, as well as Epstein-Barr virus, CMV, toxoplasmosis and herpes simplex virus (HSV).

Overall the clinical course of hepatitis A, B, C and D viruses is unchanged in pregnancy, but prevention of vertical transmission is important. Vertical transmission with maternal HAV infection is rare, and the neonate should be given immune globulin (IG) at birth. Hepatitis B virus (HBV) is screened for antenatally as the risk of vertical transmission from asymptomatic mothers is high: rates are up to 95% if mothers are hepatitis B surface-antigen and e-antigen positive. Vertical transmission usually occurs at delivery and is more likely if the HBV infection is associated with a high viral load. Several strategies including vaccination and use of HBV specific IG are in place to decrease the chance of transmission. There is sometimes a need to treat newly diagnosed pregnant women with oral anti-viral agents for her own health. All new diagnoses should be referred urgently to the local hepatitis service. There is clear guidance on management available through the Department of Health Green Book (see Further reading).

At least 6% of Hepatitis C positive pregnant women will transmit this to their baby perinatally. This risk is increased in the presence of co-infection with HIV to 15%. Elective CS may reduce the transmission risk. There is no role for treatment of HCV in pregnancy and there is no vaccine available. Screening is not routinely carried out, but should be considered in high-risk groups — mainly those with a history of injecting drug use.

Hepatitis E virus (HEV) is water-borne and transmitted faeco-orally, usually causing a mild self-limiting infection. However, in pregnancy, there is a six-fold increase in maternal mortality, especially in the third trimester, with 15% of cases leading to fulminant hepatic failure (FHF) where the mortality is 5%. The mechanism may relate to immunologic imbalance associated with a predominant T helper 2 cell subtype response and suppression of cell-mediated immunity seen in pregnancy. There is no specific treatment.

HSV (usually HSV-2) can also lead to FHF in pregnancy, often with associated pneumonitis or encephalitis. Diagnosis is made on liver biopsy and serology, and specific treatment for the mother and infant with acyclovir is available.

Rash

There are comprehensive guidelines on the management of rashes in pregnancy from the Health Protection Agency (Figure 1 and www.hpa.org.uk).

The important infections to consider in the differential diagnosis include rubella, parvovirus B19, varicella, measles, enteroviruses and infectious mononucleosis. The first three are discussed in a later section.

Measles infection in pregnancy can lead to intrauterine death and preterm delivery, although not congenital infection or damage. Indigenous measles is rare in the UK following introduction of the MMR vaccine although it is endemic in some countries. Human normal IG may attenuate measles but there is no evidence that it prevents intrauterine death or preterm delivery.

Enteroviruses (including *Coxsackie virus A, B* and *echovirus*) can cause a wide range of manifestations such as meningitis and myocarditis. Neonatal infection, especially with echoviruses, can have multisystem life-threatening complications. No vaccines are available except for poliovirus, and IG is advised for prophylaxis in exposed neonates.

Infectious mononucleosis is caused by primary Epstein-Barr virus infection with no specific risk to the fetus.

Specific pathogens

Tuberculosis

The UK and worldwide tuberculosis (TB) infection rates are rising. Incidence peaks in the childbearing years (25—34 years). In the UK, infection is most common in Asian and West-African populations. Pregnancy is thought not to change the course of TB, although it does increase preterm births, especially in the developing world. As in the non-pregnant population, transmission of *Mycobacterium tuberculosis* is via respiratory droplets. Overall 10% of those infected (initial infection is usually asymptomatic) will develop active TB, usually 1—2 years after infection. More extra-pulmonary TB is being seen with HIV co-infection, and 5—10% of pregnant women have extra-pulmonary disease (similar to the non-pregnant population). Pregnancy and the peripartum period is a common time for latent TB to reactivate. Diagnosis is by usual methods, and tuberculin skin testing is safe in pregnancy.

Management is similar to in non-pregnant patients. All four first line drugs are thought safe and have been used for many years, including ethambutol and isoniazid. Pyridoxine should be added to isoniazid therapy to prevent peripheral neuropathy. Streptomycin, however, should be avoided, as fetal eighth nerve damage has been associated in a significant number of cases. Infants born to mothers with smear-positive TB should be treated with isoniazid syrup for 6 weeks as chemoprophylaxis, and then a tuberculin skin test performed. Breast feeding can continue as normal, as minimal anti-tuberculous agents are secreted in breast milk.

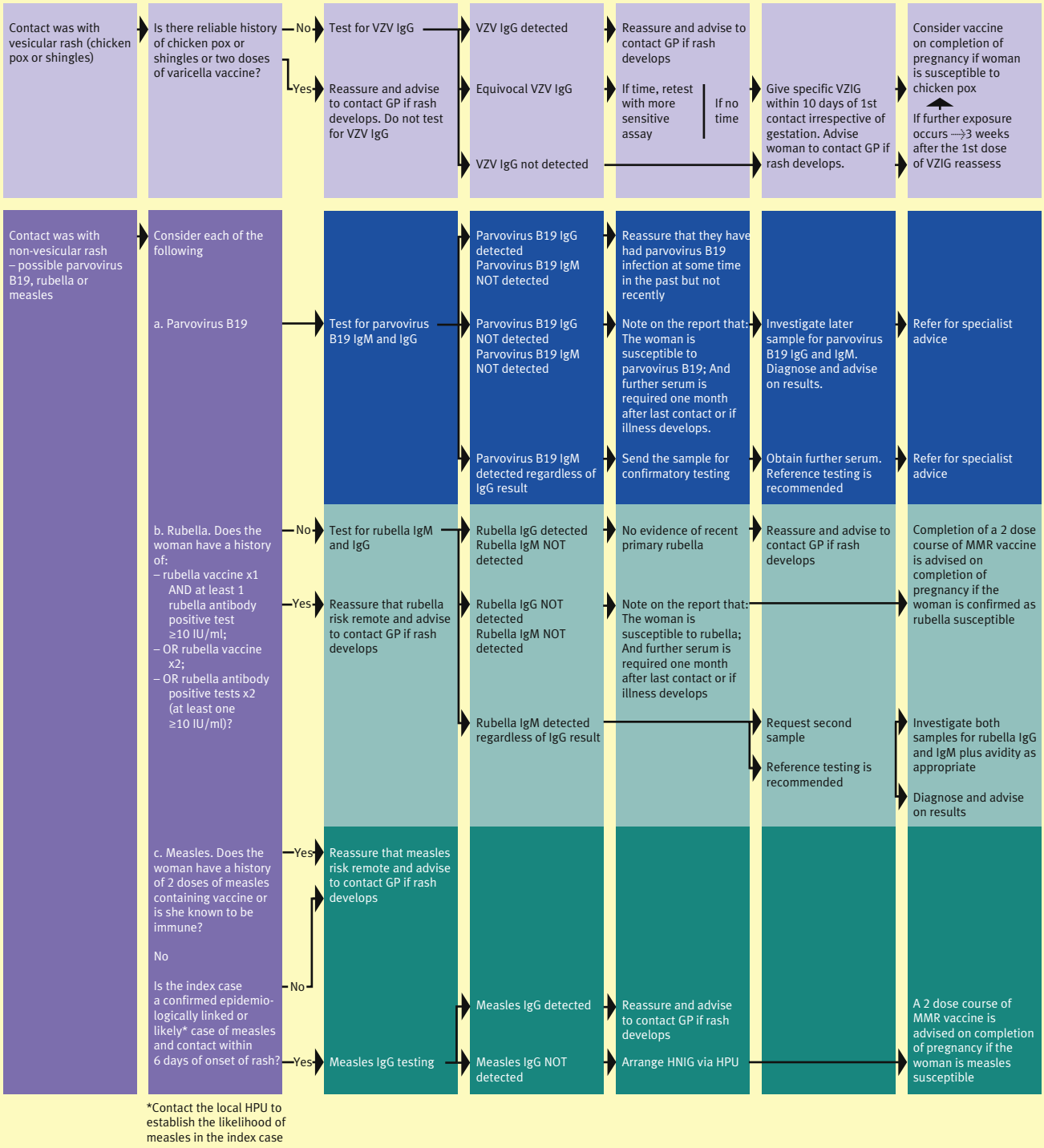
Malaria

Malaria contributes significantly to maternal mortality and morbidity in the developing world. In the UK 2000 cases are reported annually, mostly in travellers from endemic areas. Untreated falciparum malaria is life-threatening in any population, and pregnant women are more susceptible: anaemia can be severe, and there is an increase in maternal mortality, preterm birth, miscarriage and stillbirth.

Immunity to malaria is altered by pregnancy, especially in primiparous women with high parasite loads, although the risk is reduced with successive pregnancies. Drugs are used for prevention in endemic areas, with effective reduction in maternal anaemia, birth weight and possibly perinatal death. In the UK, women with malaria in pregnancy should be admitted as there is an increased risk of severe disease and hypoglycemia. Suitable regimes depend on the type of malaria and local resistance patterns, and chloroquine is the choice for *Plasmodium vivax, P. malariae, P. ovale*, and quinine for *P. falciparum*. All regimes should be supplemented with folic acid.

Malaria prophylaxis: travel to a malarial area in pregnancy should be avoided: getting malaria whilst pregnant increases the risk of miscarriage as well as being life-threatening to the mother. No antimalarial is 100% effective, and women should seek advice from a local travel clinic. There are guidelines available on the choice of agent to use if travel is unavoidable from the Royal College of Obstetrics and Gynaecology (see Further reading). Mefloquine is first line for prophylaxis after the first trimester.

Algorithm for the management of a rash in pregnancy



(With kind permission from the Health Protection Agency)

Figure 1

HIV

HIV worldwide infection is increasing. UK sero-prevalence in pregnant women is 0.21%, with over 300 HIV-infected women giving birth annually. There is an increased risk of preterm delivery, low birth weight infants and miscarriage with maternal HIV infection, worse in mothers with advanced disease and poor nutrition. Antenatal screening is done routinely in the UK.

The mother to child transmission rate in the UK is now less than 1%. This has been achieved though a variety of interventions, notably the use of antiretroviral combination therapy, a multidisciplinary approach to both the timing and method of delivery, post exposure prophylaxis for the infant, and an avoidance of breast feeding. Management of each case is highly individualized and should be done in conjunction with a team of healthcare professionals including a midwife, obstetrician, HIV specialist and a neonatologist and paediatric nurse. Some antiretroviral drugs are safe in pregnancy though currently very few are licensed. Guidelines are available (see Further reading).

Group B streptococcus (GBS)

This common vaginal commensal can lead to life-threatening neonatal effects. Of the 20% of mothers that carry it, 40–70% of infants become colonized in the first week of life. Neonatal infection can be early or late, presenting with pneumonia, sepsis, meningitis, and death in up to 10% (higher in preterm infants). As the overall UK infection rate in infants is 1%, routine screening is not currently offered. Neonatal disease is reduced by administration of intra-partum intravenous penicillin to high-risk mothers. These are identified fortuitously by high vaginal swabs performed for a variety of reasons during pregnancy, including those women complaining of vaginal discharge, those with possible preterm membrane rupture, women in preterm labour, temperature greater than 38 °C in labour, preterm PROM, ROM for more than 18 h prior to delivery, or a previously affected child.

Chlamydia trachomatis

Genital tract infection with *Chlamydia trachomatis* is common in the UK and may lead to ectopic pregnancy, preterm labour, puerperal infection and ophthalmia neonatorum. Erythromycin is the advised treatment.

Bacterial vaginosis

This STI, caused by *Gardenerella vaginalis*, may cause chorioamnionitis, preterm delivery and post-partum fevers. Treatment is with erythromycin or metronidazole.

Herpes simplex virus

Maternal genital herpes is more virulent in pregnancy. Early miscarriage (but not fetal abnormalities) may occur, and late maternal primary infection can lead to severe neonatal infection. Genital lesions, especially in primary infection, contain high viral concentrations, and transmission at delivery may exceed 41%. Neonatal herpes carries a high mortality rate. Disease can be (a) localized to skin, eyes and mouth, where death when treated is uncommon, (b) encephalitis or (c) disseminated infection with multi-organ involvement, with mortality up to 30% often with long-term neurological manifestations. Maternal infection is confirmed using viral culture or PCR, and serology differentiates between primary and recurrent infections. Primary infections should be treated with oral or intravenous acyclovir. In the UK, caesarean section is the recommended mode of delivery following primary infections in the late second and third trimesters, and discussion should be had with women presenting in labour with recurrent (secondary) herpes attacks regarding the small risk of perinatal transmission associated with vaginal birth in this situation. The risk is low, but some may choose caesarean delivery.

Infections with significant fetal malformation risks

Many infections, as detailed previously, risk fetal infection, and all maternal infections may lead to preterm delivery, but there are several important maternal infections that can lead to congenital abnormalities. These are discussed below, and summarized in Table 1.

Rubella

Symptoms of primary maternal rubella infection follow viraemia are mild and include fever, headache, joint pains, sore throat and a maculopapular rash usually appearing shortly after glandular enlargement. These non-specific symptoms make clinical diagnosis unreliable. The fetus is at high-risk of Congenital Rubella Syndrome (CRS) from infection during maternal viraemia, and significant malformations are common, seen in 80–90% survivors infected in the first trimester. Fetal abnormalities due to rubella infection in the second trimester are less common (in 15% survivors) – usually SNHL, and infection prior to conception or after 20 weeks carries minimal risk. Maternal rubella reinfection is mostly subclinical and is diagnosed by a rising antibody titre.

Suspected cases of rubella should be investigated promptly with serology testing for rising antibody titre and rubella-specific IgM as clinical diagnosis is limited.

Before rubella vaccine became available, 200–300 babies were born each year with CRS in the UK. Routine rubella vaccination for schoolgirls was introduced in England and Wales in 1970, and subsequently for susceptible women post-partum. It is a live attenuated vaccine, so is contraindicated in pregnancy, but should be offered to non-immune mothers 1 month post-partum, and pre-conceptually.

Varicella

Varicella is highly infectious from 2 days prior until 5 days following the typical vesicular rash. Fetal varicella syndrome occurs in 1% of fetuses infected before 20 weeks, especially 13–20 weeks. Note this is less than the 85% risk of rubella fetal damage hence there is currently no UK routine screening policy. Varicella is also important to recognize and treat in pregnancy as maternal complications are more severe.

Treatment in pregnancy is safe with acyclovir. If delivery is imminent, and infection occurs within 10 days of delivery, it is advisable to wait 5–7 days for passive transfer of maternal IG if possible. If not, the neonate should be given zoster IG, as there is a 20% neonatal infection risk if the mother develops clinical chickenpox in the period 5 days prior to birth until 2 days after. Neonatal infection carries a high mortality rate.

Shingles (dermatomal reactivation of latent virus) when localized carries no apparent risk to the fetus. However, it is uncertain whether dissemination, for example in an immunocompromised patient, carries a fetal/neonatal risk.

Cytomegalovirus (CMV)

Fetal CMV infection is the second most prevalent cause of mental retardation after Down syndrome. Childhood infection is common in developing countries hence leads to herd immunity, however only 50–60% of women in developed counties have positive serology. Primary maternal infection in adults may be asymptomatic or lead to infectious mononucleosis-like syndrome.

Fetal risks associated with certain maternal infections

Infection	Rubella	Varicella	Cytomegalovirus	Parvovirus B19	Toxoplasmosis
Congenital defects	Ocular defects, heart (PDA), SNHL, mental retardation	Fetal varicella syndrome: skin scars, eye defects, limb hypoplasia, developmental delay, microcephaly	IUGR, HSM, microcephaly, jaundice, chorioretinitis, intracranial calcification, 20% mortality. Late microcephaly, SNHL and developmental delay (15%)	Fetal hydrops, IUD (1st trimester). Rarely persistent neonatal infection and anaemia	Hydrocephalus, mental retardation, chorioretinitis
Trimester most at risk (% risk of defects)	First — abnormalities in 80—90% survivors; risk 13—16 weeks of SNHL	All trimesters, especially 13—20 weeks (2%)	All trimesters	First trimester	Malformations highest in first trimester. More infections near term (2% at 8 weeks versus 75% term)
Maternal effects	Arthritis	Pneumonia; increased mortality	Asymptomatic or IM syndrome	Febrile illness, erythema infectiosum, aplastic anaemia	Mostly asymptomatic, or flu-like; lymphadenopathy
Available treatment	TOP offered	ZIG to mother and neonate Acyclovir within24 h of rash onset for mother, and for infected neonates	None	Intrauterine transfusion. No vaccine	Spiramycin (cycled pyrimethamine, sulphadiazine and folinic acid)

Abbreviations: patent ductus arteriosus (PDA), sensorineural hearing loss (SNHL), intrauterine growth retardation (IUGR), hepatosplenomegaly (HSM), termination of pregnancy (TOP), infectious mononucleosis (IM), Zoster immune globulin (ZIG).

Table 1

Primary infection, reactivation, or reinfection with a different strain of CMV may lead to intrauterine infection, although the fetus is rarely affected in cases of reactivation.

Primary infection leads to transplacental fetal infection in 40% of cases, and fetal sequelae may occur over a wide timescale. Up to 7% will present at birth with defects (see Table 1). The mortality is 20% in this group, and a further 15% will have abnormalities found later at follow-up.

In cases of suspected maternal infection, blood serology, ideally with a paired sample from booking to compare rising antibody titre, noting that circulating IgM may persist for months. When confirmed, fetal infection should be proven by culture and PCR of amniotic fluid at amniocentesis. Serial fetal ultrasound is available to identify suggestive features such as ventriculomegaly and intracranial calcification, although no findings are specific. It must be remembered that most infected neonates will infact be unaffected. There is no specific treatment, although a vaccine is in development, and screening for maternal immunity is therefore not routine in the UK.

Parvovirus B19

Parvovirus B19 infection is common with 50—60% of adults having been infected. Infection in the first 20 weeks of pregnancy can lead to intrauterine death and fetal hydrops. These consequences usually occur 3—5 weeks after the onset of maternal infection, but can be later. There is no evidence to suggest reinfection is a risk to the fetus. No vaccine or preventive measures are available, and an increased incidence occurs every 3—4 years, often in schoolchildren.

Toxoplasmosis

Maternal infection is rare (two per 1000 in the UK; more common in France), and flu-like symptoms and lymphadenopathy occur in up to 15% of infected women. Fetal infection probably depends on the gestational age at maternal seroconversion. A French study showed there were more congenital abnormalities (see Table 1) with early maternal infections, and more fetal infections with seroconversion at term.

Diagnosis is confirmed by amniocentesis, chorionic villus sampling or fetal blood sampling, and US findings of intracranial calcification, hepatomegaly and placental thickening are late and non-specific. Treatment with spiramycin from time of maternal infection may reduce fetal infection, and therefore congenital abnormalities. In late (after 32 weeks) high-risk fetal infections, 3-week cycled courses of pyrimethamine, sulphadiazine and folinic acid may be added.

Syphilis

Maternal infection with the spirochaete *Treponema pallidum* has increased in recent years. Fetal infection can occur at any stage, but most often in primary (90%), secondary and early latent infections. Most infected women are asymptomatic and positive

serology is detected at antenatal screening. Maternal infections treated with high-dose penicillin will reduce the risk of fetal infection. 25% of fetal infections result in preterm labour, and 25% in fetal loss. In survivors, congenital syphilis may result with polyhydramnios, hepatomegaly, osteochondritis, purpura and late interstitial keratitis. Fetal infection is suggested by antigen testing of amniotic fluid or fetal blood, although these have a poor negative predictive value.

Listeria monocytogenes

Listeriosis is caused by *Listeria monocytogenes*, a gram-positive bacillus, and although an unusual infection, may have serious adverse outcome in pregnancy. There are about 20 case of Listeria associated with pregnancy in the UK per year. It is food-borne, from unpasteurized dairy products, and pregnant women should avoid such high-risk foods. It can survive at low temperatures (such as the fridge) on raw vegetables hence the importance of washing food in pregnancy. Maternal symptoms can be asymptomatic, or with flu-like symptoms, and can range from mild to severe with ARDS. The diagnosis is based on a high index of clinical suspicion, and on positive gram stain from maternal blood, liquor or neonatal samples.

Maternal infection can lead to miscarriage, premature labour, and if the infant survives, to perinatal listeriosis. Congenital listeriosis has also been reported following transplacental passage, and can lead to fetal hydrops. Treatment is with high-dose ampicillin and gentamicin.

Conclusion

Infections during pregnancy are usually self-limiting however awareness is needed to identify those leading to significant maternal and fetal morbidity and mortality. Screening and vaccination programs are important. Investigation and management of infection may be complex and the multidisciplinary approach is essential, involving the obstetric team, as well as fetal medicine, genitourinary and critical care physicians. ◆

FURTHER READING

Antenatal Routine Care for the healthy pregnant woman, NICE Antenatal Care Clinical Guideline 6, London October 2003.

Hepatitis guidelines: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_108820.pdf.

HIV guidelines: www.bhiva.org.

Mackenzie, Lever. Management of sepsis. *BMJ* 2007; **335:** 929–32.

Malaria prophylaxis: http://www.nathnac.org/pro/misc/pdfs/RCOGPreventionMalariaPregnancy0410.pdf.

Maternal mortality. *Saving Mothers Lives: Reviewing maternal deaths to make motherhood safer: 2006–2008. The eighth report of the Confidential Enquiries into Maternal Deaths in the UK*, **118**. London: BJOG, 2011. 1–203.

Nelson-Piercy C. Handbook of Obstetric Medicine. 4th edn, *Obstet Med* 2011; **4:** 87, doi:10.1258/om.2011.110023.

Royal College of Obstetricians and Gynecologists. Chickenpox in pregnancy: Guideline No 17. London: RCGOG, September 2007.

Royal College of Obstetricians and Gynecologists. Genital herpes in pregnancy: Guideline No 30. London: RCGOG, September 2007.

Royal College of Obstetricians and Gynecologists. HIV in pregnancy: Guideline no 39. London: RCGOG, April 2004.

Royal College of Obstetricians and Gynecologists. Preterm prelabour rupture of membranes: Guideline No 44. London: RCGOG, November 2006.

Smiall F. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Pregnancy and Childbirth group. *Cochrane Database Syst Rev* 2005; **1**.

Tookey P. Rubella in England, Scotland and Wales. *Euro Surveill* 2004; **9**. National congenital Rubella Surveillance Program, Institute of Child Health, London, England.

WHO guidelines for treatment of severe H1N1 Influenza A: http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf.

Practice points

- Most maternal infections do not harm the fetus
- All rash illnesses should be referred for specialist assessment
- Maternal obstetric sepsis may present with non-specific symptoms and signs, and run a fulminant course
- Obstetric sepsis remains a significant cause of maternal mortality and should be identified early and managed aggressively
- The investigation of infections that can affect the fetus should be appropriate for both mother and fetus, usually in or in consultation with a feto-maternal medicine unit
- Screening is important for HIV as interventions exist to reduce vertical transmission