14.16 Fetal effects of maternal infection 2678

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ESSENTIALS The fetal effects of maternal infection in pregnancy can be broadly categorized as follows (these are not mutually exclusive): (1) transplacental infection causing fetal malformation (e.g. syph- ilis, rubella); (2) transplacental infection causing severe in utero illness (e.g. parvovirus); (3) neonatal infection/carrier status as a result of transplacental or intrapartum infection (e.g. HIV, Varicella zoster); such neonatal infection may be severe; (4) preterm delivery, late miscarriage, perinatal death, and cerebral palsy at term delivery are more common in the presence of in utero and placental infection (chorioamnionitis) (e.g. group B streptococcus). Viral Human immunodeficiency virus—transplacental transmission oc- curs most frequently during delivery and breastfeeding. Prevention is achieved by the use of antiretrovirals, mode of delivery planned according to the viral load at 36 weeks, and the avoidance of breastfeeding. Parvovirus—transplacental infection can cause fetal anaemia and cardiac failure. Severely anaemic fetuses can be transfused in utero. Cytomegalovirus—transplacental infection is variable, but severe neurological damage, impaired growth and deafness may follow. Herpes simplex—intrapartum infection can cause severe neonatal illness following a recent primary attack and is prevented by cae- sarean section. Varicella zoster—severe neonatal illness can follow late pregnancy disease; maternal disease is often severe. Hepatitis B—transplacental transmission usually causes chronic carrier status and is reduced by neonatal active and passive immunization. Zika virus—infection in the first trimester can cause microcephaly and ocular abnormalities Other Bacterial vaginosis—associated with preterm delivery. Treatment of women with a previous preterm delivery may reduce the risk of recurrence. Streptococcal infection—group B can cause severe neonatal illness following intrapartum infection and is reduced by intrapartum anti- biotics for either screen positive women or those with intrapartum risk factors. Chlamydia—associated with preterm delivery and neonatal conjunctivitis. Syphilis—although rare in the West, syphilis is endemic in many countries, with transplacental infection causing congenital syphilis and perinatal death. Toxoplasmosis—transplacental infection can cause severe fetal disease; treatment may prevent transmission and reduce disease severity. Malaria—a major cause of neonatal mortality in parts of Africa; prevention is with nets and chemoprophylaxis. Severe malaria is usually treated with artesunate. Introduction Immunity is mildly suppressed in pregnancy, and the fetal

immune system is developmentally immature. Infections in pregnancy can therefore be devastating both for the mother, as is occasionally seen with varicella, and for the fetus, as exemplified by congenital infec- tions such as those caused by rubella, cytomegalovirus, syphilis, and toxoplasmosis. Preterm delivery accounts for 80% of neonatal unit cot days, is the single most important contributor to long-term handicap, and is a major cause of perinatal mortality. In addition to the specific effects of individual infections, infection in pregnancy is an important risk factor for these adverse outcomes. Infection is implicated in over 50% of preterm deliveries and considerably worsens the prognosis for the neonate at any given preterm gestation. The vaginal pathogens, including bacterial vaginosis and group B streptococcus are varied and only intermittently associated with adverse outcomes: it is likely that cervical integrity is both affected by bacteria and affects the access of bacteria to the uterus. Non- 'ascending' infection may also be important, with periodontal dis- ease associated with an increased risk of preterm delivery. At term, clinical or histological chorioamnionitis are associ- ated with a large increase in the risk of neonatal death, neonatal 14.16 Fetal effects of maternal infection Lawrence Impey

 encephalopathy, and cerebral palsy. The relative contributions of infection and an inflammatory response associated with other risk factors (e.g. pre-eclampsia) are not known, although the limited but potentially devastating role played by bacteria such as group B streptococcus is clearly understood. Currently, with the exception of group B streptococcus, it remains unknown whether the use of anti- biotics or antipyretics reduces the associated risks. The most important infective organisms in pregnancy are de- scribed in this chapter: detailed discussion of their pathology and features in adults are described in Section 8. Viral infections Human immunodeficiency virus (HIV) Human immunodeficiency virus (HIV) HIV/AIDS is caused by the HIV-1 and HIV-2 retroviruses. In 2017, there were 18.2 million women aged >15 years living with HIV worldwide, of whom 1.5 mil- lion were pregnant. Ninety one percent of HIV-positive pregnant women live in sub-Saharan Africa, where up to 40% of the women attending antenatal services in some areas are HIV positive. HIV and complications related to pregnancy are two of the leading causes of death globally for women of reproductive age. In 2016, an esti- mated 89 400 people were living with HIV infection in England; the prevalence of HIV infection among pregnant women in the UK is approximately 2 per 1000 women. The predominant mode of infec- tion is heterosexual sexual contact, with a risk of infection per epi- sode of <1%. Universal antenatal HIV screening was implemented in the United Kingdom in 2000, and by 2014 the uptake was estimated to be 97.3%, with 0.15% testing positive (0.03% new diagnoses). In 2009–2014, 99.2% of all diagnosed pregnant women in the UK had received some form of antiretroviral treatment before delivery. The increase in diagnosis and treatment, as well as the implementation of successful obstetric and neonatal interventions has led to a de- cline in the incidence of mother-to-child transmission (MTCT) in the UK, from 25.6% in 1993 to 0.27% in 2012–2014. In developing countries where there are large service gaps, however, the incidence of MTCT remains as high as 20–30%. Pregnancy does not affect the progression of HIV, but the effect of HIV on pregnancy remains unclear. There is some evidence sug- gesting an increase in the rates of pre-eclampsia and gestational dia- betes. Maternal HIV infection is also associated with increased risks of preterm delivery, small-for-gestational-age, low birth weight and stillbirth. These effects may be higher in women on highly active antiretroviral therapy (HAART), especially if ART was initiated be- fore conception, although further studies are required. MTCT occurs largely, but not exclusively, during delivery or breastfeeding. Its prevalence is highest in sub-Saharan Africa, as a result of low rates of diagnosis and treatment, poor availability of obstetric care, and the high

prevalence of breastfeeding. The issues surrounding breastfeeding in the developing world are complex, as its avoidance is associated with a high incidence of infant death, particularly due to scarcity of safe drinking water. Other factors influencing MTCT include concomitant sexually transmitted infec- tions (especially Hepatitis C), preterm delivery, and high viral loads. Practical prevention of MTCT needs to vary according to re- sources and availability of healthcare. A multidisciplinary approach is required to optimize obstetric and neonatal management. Under ideal circumstances, combination therapy using HAART is advised; zidovudine alone is less effective and allows the emergence of re- sistant strains. If not already taking combined anti-retroviral therapy (cART), HIV-positive pregnant women should start ART during pregnancy, at the latest by week 24, and continue lifelong. Women should be screened and treated for other sexually transmitted infections early in gestation and again at 28 weeks. Antenatal blood tests include renal and liver function tests to look for drug toxicity. In women con- ceiving on cART, the CD4 count and viral load should be checked at baseline and at 36 weeks and delivery. In women who commence cART in pregnancy, these are checked as per routine initiation of cART, at least once every trimester, at 36 weeks and at delivery. The treatment regimen should be modified if viraemia is not suppressed. The mode of delivery should be individualized and is largely de- termined by the viral load at 36 weeks. Two large European cohort studies have shown MTCT rates of less than 0.5% in women with viral loads less than 50 copies/ml irrespective of the mode of de- livery. This has led to an increase in planned vaginal deliveries in this group in the UK. Intrapartum strategies have included the avoid- ance of early amniotomy, fetal blood sampling, and the use of fetal scalp electrodes; low-cavity forceps should be used in preference to Ventouse if necessary. Planned caesarean section at 39 weeks re- mains the preferred modality of delivery in women with viral loads more than 50 copies/ml, those on zidovudine monotherapy, and in the presence of Hepatitis C co-infection. Antiretroviral treatment should be given to the neonate for 2–4 weeks, depending on ma- ternal viral load at delivery. Breastfeeding should be avoided and cabergoline offered to suppress lactation. In developing countries where resources are scarce, a different strategy is required: caesarean section is less readily available and associated with higher operative and future obstetric risks, and the avoidance of breastfeeding has more serious implications. In the absence of triple therapy, zidovudine monotherapy ante- natally after 14 weeks, with the addition of single-dose nevirapine and lamivudine in labour, or even a single dose of nevirapine admin- istered in labour are among less effective alternatives. Amniotomy is avoided as the rate of MTCT is directly related to the duration of ruptured membranes in women with high viral loads. Breastfeeding is exclusive, limited to six months, and combined with antiretroviral treatment. Rubella Up to 20% of women in the United States, and more in developing countries, are nonimmune, hence small outbreaks of rubella still occur. Immunization programmes vary worldwide; in the United Kingdom rubella forms part of the measles, mumps, and rubella (MMR) vaccination in early childhood and most women are im- mune: fewer than 10 affected neonates are born each year in the United Kingdom. The incubation period is 14–21 days, with in- fectivity seven days before and seven days after the appearance of the characteristic rash, which is preceded by a short prodrome of low-grade fever, headache, malaise, and lymphadenopathy. Arthritis and arthralgia occur in up to 70% of adult women, and rare ma- ternal complications are thrombocytopenia, acute post-infectious encephalitis, myocarditis, Guillain–Barré syndrome, relapsing en- cephalitis, optic neuritis, bone marrow aplasia, and progressive panencephalitis.

 The fetus is at greatest risk during the first trimester, when 90% will be affected, either by miscarriage or congenital rubella syndrome. This

consists of congenital heart disease (especially pulmonary ar- terial hypoplasia, patent ductus arteriosus, and coarctation of the aorta), learning difficulties, ocular defects such as cataracts, glau- coma, and microphthalmia, and sensorineural deafness. Between 12 and 16 weeks the sequelae are less severe, with sensorineural deaf- ness predominating. At 25 weeks vertical transmission is approxi- mately 25%, rising to 100% at term, but the fetus is almost invariably unaffected. Congenital rubella can only be prevented by immunization. Immunity is no longer routinely checked in early pregnancy. If IgG is absent, maternal IgM suggests recent infection. Termination of pregnancy may be offered where infection has occurred in the first trimester. In the absence of IgM, postnatal vaccination is recom- mended. The vaccine is live, attenuated, and therefore contraindi- cated in pregnancy, although inadvertent administration has not led to recorded problems. Parvovirus The parvovirus B19 is the only pathogenic parvovirus in humans. Infectivity is high and via respiratory secretions, often from children. More than 50% of adults in Western countries are immune; 0.25% of women are infected in pregnancy, but infection can be epidemic. Viraemia appears about seven days after infection and has disap- peared within a few days, before symptoms occur. The classic ‘slapped cheek’ rash is not invariable and most have an arthralgia; 50% of adults have no symptoms. Pregnancy does not alter these symptoms. Infection in pregnancy has an approximately 30% rate of fetal infection; the excess loss rate in pregnancy is 10%, largely with ex- posure before 20 weeks’ gestation. A characteristic effect is due to the parvovirus binding to the P antigen present on erythrocytes, erythroblasts, and myocardium. This can cause a predominantly aplastic anaemia that is of minimal significance in healthy children or adults. By contrast, the fetus is vulnerable, largely because of the short half-life of fetal red blood cells and the need for erythropoiesis, and it may develop a severe aplastic anaemia with a variable but oc- casionally severe thrombocytopenia. This is a cause of nonimmune hydrops (Fig. 14.16.1c), exacerbated in some cases by cardiac dys- function, which is self-limiting in more than 50% of cases but fatal in the rest. Fetal death typically occurs three to six weeks after infection and is very unusual more than 18 weeks afterwards. Management of the woman infected by parvovirus involves ultra- sound scans assessing the middle cerebral artery, peak systolic vel- ocity which is increased in anaemic fetuses: initially every week, and up until four months after infection, after which the mother can be reassured that her risk of fetal loss is extremely low. The anaemic fetus can be given an in utero blood transfusion. Cytomegalovirus Cytomegalovirus is the commonest congenital infection in devel- oped countries. Immunity is present in up to 75% of women; less in higher socioeconomic classes or in developing countries. Infection in pregnancy occurs in about 1%. Maternal infection is usually asymp- tomatic but can cause an infectious mononucleosis-like illness. Vertical transmission occurs during pregnancy following 40% of primary infections and less than 1% of secondary recurrences. After primary infection, 5–15% of neonates are symptomatic, and of these more than 80% develop severe neurological sequelae, including (a) (b) (c) Fig. 14.16.1 Antenatal ultrasound scans: (a) fetal head showing ventriculomegaly secondary to congenital toxoplasmosis; (b) fetal abdomen showing intrahepatic calcification seen in congenital varicella infection; (c) fetal abdomen showing ascites in parvovirus infection. Parvovirus in pregnancy is encountered either during investigation of fetal hydrops, or where there has been maternal infection or contact with an infected individual. For the former, the diagnosis is made when the hydropic fetus is established to be anaemic, usually by the finding of a raised peak systolic velocity in the fetal middle cerebral artery, and by exclusion of other causes of hydrops. Maternal blood will usually show IgM; if IgG is present, a stored early pregnancy booking sample can be checked for comparison, although viral identification by PCR of a fetal blood sample is more reliable. An in utero transfusion greatly improves survival and is given if the degree of anaemia appears to be

increasing and the fetal state worsens. This involves injection of high haematocrit irradiated cytomegalovirus-negative blood into the umbilical vein, usually at the cord insertion. When the disease appears to be severe, an in utero platelet transfusion is recommended by some because of the potential for thrombocytopenia and reports of severe and fatal fetal bleeding following in utero transfusion. Long- term follow-up of successfully treated babies is reassuring, but there are reports both of fetal loss at transfusion and of severe cerebral damage following very severe fetal anaemia, as well as in utero demise from cardiac failure.

14.16 Fetal effects of maternal infection 2681 intellectual impairment and sensorineural hearing loss. Even asymptomatic infants have a 5–15% risk of hearing impairment. Overall, the chance of normal childhood development without evi- dence of fetal damage is approximately 75%. Recurrent cytomegalo- virus infection is less often vertically transmitted, with sensorineural deafness most common among affected infants. The outcomes of primary cytomegalovirus infection in pregnancy are shown in Fig. 14.16.2. Ultrasound abnormalities, particularly intracranial or hepatic calcifications, cerebral ventriculomegaly, oligohydramnios, and intrauterine growth restriction are detected in only 20%. Cytomegalovirus is diagnosed in pregnancy usually because IgM is found incidentally, although it may be detected as part of the in- vestigation of a fetus with abnormalities (e.g. small for gestational age, cerebral ventriculomegaly, or where the fetal bowel appears echogenic to ultrasound). Cytomegalovirus IgM is long-lasting and its identification in pregnancy may predate the pregnancy, hence a negative retrospectively tested booking sample, or low IgG avidity, or rising IgG or IgM titres are required to confirm maternal infec- tion. Vertical transmission is detected using amniocentesis and polymerase chain reaction (PCR), which need to be performed no earlier than 20 weeks' gestation and six weeks after maternal infec- tion, or in the presence of ultrasound abnormalities (which have multiple other causes), to exclude fetal infection. Ultrasound abnor- malities, high viral load, and thrombocytopenia are associated with more severe sequelae. However, prediction of severe disease is still imprecise. Administration of hyperimmune globulin shows promise in re- ducing vertical transmission rates, but there is no effective in utero therapy and termination of pregnancy may be offered: currently in the United Kingdom this can be performed late in the pregnancy. Intravenous ganciclovir given to the infant reduces hearing loss in the most severely affected. Cytomegalovirus screening is currently not recommended because of the risk of amniocentesis and absence of proven in utero treatment. Herpes simplex (HSV) HSV-2 is the predominant cause of genital herpes, but in up to 30% of cases it is HSV-1 that is responsible. Primary infection in preg- nancy occurs in 2% of susceptible women. This is usually asymp- tomatic, but primary herpes may be characterized by genital pain and ulceration, discharge, dysuria, lymphoedema, and systemic symptoms. The development of vesicles may occur for the first time in a woman previously infected: it does not necessarily imply recent transmission. Herpes simplex is transmitted vertically at vaginal delivery, but very rarely during pregnancy. Transmission is up to 40% in ac- tive primary infection, with the greatest risk in late pregnancy, but nearer 1% with active recurrent herpes because of passive fetal immunity. Nevertheless, most neonatal herpes occurs in women without a history and may be acquired postnatally (25%). It is rarer in the United Kingdom (3/100 000 live births) than in the United States or Europe, but causes severe illness including encephalitis and death, particularly in preterm neonates. Where characteristic vesicles are seen, viral swabs are taken. The absence of maternal IgG to HSV-1 and HSV-2 confirms a primary infection. Herpes simplex is treated with aciclovir 400 mg three times daily for five days, usually continued until delivery if diag- nosed in the third trimester. This reduces symptoms, recurrence, and viral shedding. Caesarean delivery is recommended if delivery occurs within six

weeks of the diagnosis of a primary infection, irre- spective of whether lesions are visible. If the infection has occurred more than six weeks previously, and no lesions are visible, vaginal birth is appropriate. This should be performed before, or as soon as possible after the membranes have ruptured. If vaginal delivery is un- avoidable or the membranes have been ruptured for more than four hours, the mother and neonate are usually treated with intravenous aciclovir. Caesarean delivery is not advised if primary infection has occurred earlier in the pregnancy or where there is asymptomatic recurrent herpes. Screening and searching for asymptomatic viral shedding is not advised. Varicella zoster In Western countries, more than 90% of adults are immune to varicella zoster virus, with infection only occurring in 3 per 1000 pregnancies. In developing countries, many more are nonimmune. Transmission is by respiratory droplets and personal contact with the vesicles. Primary infection causes chickenpox; reactivation of the virus that has lain dormant in sensory nerve root ganglia causes shingles. The incubation period is 10–21 days, infectivity being from 48 h before the rash appears to when all the vesicles are covered. Primary infection in pregnancy may be severe. Maternal shingles is not associated with neonatal risk. 1–2% primary infection in pregnancy 40% transmission to fetus 10–15% newborns have clinical disease 85–90% newborns are asymptomatic 10% develop normally 90% have sequelae Usually severe 90% develop normally 10% have sequelae Usually sensorineural deafness Fig 14.16.2 The outcome of cytomegalovirus infection in pregnancy.

Section 14 Medical disorders in pregnancy 2682 The principal risk to the fetus is with primary infection in late pregnancy, when varicella infection of the newborn occurs in 50% and is associated with a neonatal mortality approaching 30%. Infection between 28 and 36 weeks' gestation, in the absence of pre- term delivery, does not have sequelae. Before 28 weeks, however, 1–2% of fetuses develop the fetal varicella syndrome, characterized by neurological, optical, and limb anomalies. Ultrasound findings around five weeks after infection may also show polyhydramnios and echogenic foci in the fetal liver (Fig. 14.16.1b). Where a pregnant woman is exposed to chickenpox or shingles, her IgG should be checked and if present indicates immunity. A nonimmune mother with significant exposure should be given vari- cella zoster immune globulin (VZIG) within 10 days, and should be regarded as infectious for 4 weeks. If clinical chickenpox develops, aciclovir is recommended, IV if maternal illness is severe. Before 28 weeks, careful fetal ultrasound evaluation is required; the use of amniocentesis is controversial. In later pregnancy, VZIG is given to the neonate if delivery occurs between five days after and two days before maternal infection. Vigilance for neonatal infection is required: this is treated with aciclovir. Hepatitis B Less than 1% of pregnant women in Western countries are HBsAg positive, although the incidence is rising; in parts of Africa and Asia the rate is 25%. Vertical transmission can occur throughout pregnancy and is particularly important because 90% of infected neonates become chronic carriers (in contrast to adults, 10% of whom become chronic carriers) that are both infectious and at risk of liver disease. The risk of transmission relates to maternal viral antigen status: in HBsAg positive/HBeAg negative mothers the risk is 5–20%; in HBsAg positive/HBeAg positive it is 70–90%. Transmission is higher with high activity of replication or high viral load. Targeted screening only identifies about half of chronic carriers, so universal screening has been adopted in developed countries. Vertical transmission can be reduced by more than 90% by active neonatal immunization, using 0.5 ml hepatitis B vaccine. This is recommended to all infants born to HBsAg positive mothers; additional passive immunization (200 IU of hepatitis B immunoglobulin within 12 h of birth) for infants born to HBeAg positive or HBsAb negative mothers is also advised. For women with a very high viral load, the European Association for the Study of the Liver now

advises treatment with antiviral agents during pregnancy, starting at 32 weeks. The World Health Organiza tion recommends universal vaccination in countries with high prevalence. Hepatitis C Worldwide, 3% of pregnant women have been infected with hepa- titis C virus (HCV), but the figure is up to 50% in HIV-positive women. The principal risk factor in the United Kingdom, where about 0.5% of women have been infected, is intravenous drug abuse, and sexual transmission is unusual. Hepatitis C leads to chronic hepatitis in about 80%; progression is insidious and most pregnant women are asymptomatic. Vertical transmission of HCV occurs in approximately 5% but is higher with higher viral loads and with coexisting HIV infection. Transmission is not thought to be signifi- cantly affected by mode of delivery. Transmission by breast feeding is unlikely. Elective caesarean section, formula feeding, and admin- istration of immune globulin do not reduce vertical transmission to the neonate. Maternal antibodies may persistent for months, hence PCR is used to confirm infection in infants. Infected infants usually remain viraemic and prone to chronic hepatitis. Zika An outbreak of Zika virus, a flavivirus transmitted primarily through the bite of an infected Aedes species mosquito, was identi- fied in Brazil in early 2015 and has spread rapidly in the Americas. Zika infection during pregnancy has been linked with micro- cephaly, with strong evidence of causality, most notably by demon- stration of Zika virus in the brains of affected fetuses and infants. The estimated risk of microcephaly following infection in the first trimester is uncertain, but probably in the range 0.9–13.2%: there does not appear to be enhanced risk with infection in the second or third trimesters. Many (35%) babies with microcephaly also have ocular abnormalities, most commonly focal pigment mot- tling, chorioretinal atrophy, and optic nerve abnormalities. It is not known whether ocular manifestations occur after congenital Zika virus infection in infants who do not have microcephaly. The long- term prognosis of infants with Zika virus-induced microcephaly is likely to be poor. Bacterial diseases Bacterial vaginosis This occurs when there is an overgrowth of anaerobic organisms such as Gardnerella vaginalis and Mycoplasma hominis and charac- terized by excessive Gram-negative bacilli and cocco-bacillary or- ganisms compared to lactobacilli on Gram staining. The prevalence varies from 5 to 20%, depending much on the diligence with which the diagnosis is sought. Bacterial vaginosis is not sexually trans- mitted but is associated with sexually transmitted infections and is rare before the onset of sexual activity. Three of four Amsel’s criteria are required for diagnosis: a thin white homogeneous discharge, clue cells, raised vaginal pH (>4.5), and a positive ‘whiff test’ (fishy odour when 10% potassium hydroxide is added to the discharge). At least 50% of women with bacterial vaginosis have no symptoms, but an offensive, thin white discharge is often found. Bacterial vaginosis is associated with late miscarriage and preterm birth, a major cause of neonatal mortality and morbidity, possibly because of a depletion in lactobacilli. There is little evidence that treatment, usually with clindamycin, reduces the incidence of pre- term birth; however, it does appear to do so when given prior to 20 weeks in women with a history of prior preterm birth or late mis- carriage. The use of other methods to promote lactobacillus growth merits investigation. Streptococci Group A streptococci (Streptococcus pyogenes) are an important cause of puerperal sepsis worldwide but may also cause chorioamnionitis and late miscarriage or preterm labour. Group B streptococci (Streptococcus agalactiae) are an important cause of neonatal sepsis in the first week: early onset infection. Approximately 25% of pregnant women are colonized by group

 B streptococcus, usually without symptoms, although maternal urinary tract infection is not uncommon. Group B streptococcus is associated with preterm delivery but it is ascending infection at the time of delivery that is best understood. Although 70% of neo- nates born to carriers are colonized, only 1–2% will develop dis- ease of

chorioamnionitis and fetal infection leading to early onset neonatal streptococcal sepsis. The incidence of this is 0.5/1000 live births in the United Kingdom and 0.24% in the United States (2010). The mortality is 7% at term and 18% preterm. Intrauterine infec- tion can also occasionally cause antepartum stillbirth. Infection usually but not always occurs following rupture of the amniotic membranes: risk factors are prematurity, prolonged rupture of the membranes, intrapartum maternal fever, heavy colonization, low maternal antibody levels, and a previously affected infant. Intrapartum high-dose intravenous penicillin greatly reduces early onset neonatal disease. Late onset (after the first week) group B streptococcus infection has an incidence of 0.35/1000 live births and is not altered by intrapartum antibiotics. Antibiotic resistance is virtually zero, but penicillin-allergic women are a problem: 12% of group B streptococcus are resistant to clindamycin. Universal screening is performed in many countries; in the United States, this has been followed by a fall in the incidence from 1.5/1000 live births in 1993 to 0.24/1000 in 2010. Women are screened at 35–37 weeks with vaginal and anal swabs and given high-dose penicillin intrapartum if they are carriers. If there was group B streptococcus in the urine at any time, or a previously infected infant, they are also treated. This policy leads to approximately 25% of all pregnant women being treated, with 86% of cases of sepsis prevented. In the United Kingdom, a risk-based strategy is recommended: women are treated if they have a previous history, intrapartum fever, are in con- firmed preterm labour, or where the membranes have been ruptured for more than 18 h. This leads to at least 70% of neonatal sepsis being prevented by treating approximately 18% of women. The arguments against universal screening are concerns with anaphylaxis, the low UK incidence of early onset disease, the lack of randomized con- trolled trial evidence, and the potential medicalization of pregnancy. A result of the UK policy is increased monitoring and treatment of more newborns. Recent advances include rapid diagnostic tests, but unless en- riched samples are tested the reported sensitivity is not as good as with swabs, and these have not yet been widely adopted. Vaccination against group B streptococcus is under development using a triva- lent polysaccharide-protein conjugate vaccine that could ultimately be offered to all pregnant women. Listeria Infection is from salads contaminated with animal faeces, under- cooked meats, unpasteurized milk, soft cheeses, some fruit, hummus, and patés. In the United Kingdom the incidence is up to 5 per 100 000 live births. Worldwide the incidence has fallen as a result of public health campaigns about the likely source of infection. Maternal disease manifests as bacteraemia, with fever, sore throat and headache: diarrhoea, pyelitis, and backache may also occur. It is treated with ampicillin with an aminoglycoside for synergy. Infection of the fetus occurs transplacentally. Before 24 weeks' gestation, this usually results in miscarriage; after 24 weeks, neonatal mortality is approximately 20%. Chlamydia Chlamydia trachomatis is the most common sexually trans- mitted infection, with up to 7% of pregnant women being in- fected, depending on age, marital status, and socioeconomic class. Infection is mostly asymptomatic. Maternal infection, particularly if recently acquired, is associated with a fourfold increase in se- vere preterm delivery. Treatment reduces but does not eradicate these risks. Neonatal conjunctivitis occurs in up to 50% of neo- nates exposed to chlamydia, with a smaller proportion developing pneumonia. The identification of maternal infection warrants referral to a genitourinary medicine clinic, with contact tracing for treatment of sexual partners. Erythromycin is effective, but a single dose of azithromycin (1 g) ensures compliance and is also known to be safe. Tetracyclines are contraindicated in pregnancy as they cause tooth discoloration in the child. Reinfection rates are high and repeat testing is advised after at least three weeks to ensure a cure has been achieved. Screening or even prophylaxis of all mothers following termination is cost-effective, but routine screening in pregnancy using urine PCR should currently be limited to those at risk of infec-

tion, who are also at increased risk of preterm delivery. Gonorrhoea Neisseria gonorrhoea is endemic in many developing countries, and having fallen to low rates in many areas of the developed world by the early 1990s is now gradually increasing again. Pharyngeal and disseminated systemic infection with fever, rash, and septic arthritis are more common in pregnancy, but salpingitis is rare. Cervical cul- ture detects most infections; PCR testing is expensive and does not enable antibiotic sensitivity testing. As with nonpregnant women, 80% are asymptomatic. Gonococcal cervicitis is associated with a fourfold increase in pre- maturity and chorioamnionitis. Further, 40% of neonates exposed to gonorrhoea at delivery will develop ophthalmia neonatorum. Gonococci have also been implicated in post-partum and post- abortion endometritis and salpingitis. Treatment is best with a single intramuscular dose of ceftriaxone (250 mg). Disseminated infection warrants intravenous therapy. Penicillinase-producing strains are common. The patient should be screened for other sexually transmitted infections and antichlamydia therapy is often given at the same time. A test of cure should be taken at least three days after antibiotics. Because of the frequency of infec- tion and the serious risks, screening is warranted in high-risk groups such as those undergoing first-trimester termination. Syphilis The incidence of infection in pregnancy is 0.02% in the United Kingdom, but in Africa, Southeast Asia, and Russia it is endemic. Pregnancy does not alter the clinical manifestations. Screening with nontreponemal tests (e.g. the venereal disease research laboratory test) is routine in many countries, including the United Kingdom. Sensitivity is highest in secondary syphilis and lowest early in the in- fection, and false-positive results occur with concomitant infections or autoimmune disease. Vertical transmission is predominantly transplacental, occurring in up to 90% of untreated women, particularly those with early

 disease. Most affected pregnancies result in congenital syphilis, miscarriage, preterm delivery, or perinatal death. Ultrasound examination of the infected fetus may be normal or show hepato- megaly and other abnormalities. At birth, babies exhibit rhinitis, osteitis, and skin bullae. Hutchinson’s triad of abnormal teeth, interstitial keratitis, and sensorineural deafness arise later in the untreated child. Syphilis is usually diagnosed in pregnancy after the development of suggestive symptoms or a positive screen. A positive venereal disease research laboratory test should be confirmed with a spe- cific treponemal test (e.g. FTA-ABS). Treatment is with two intra- muscular doses of benzyl penicillin (2.4 MU, one week apart). In true penicillin allergy, a 5- to 10-day regimen of high-dose oral ceftriaxone is recommended. Venereal disease research labora- tory test titres should fall until undetectable or less than one in four, otherwise retreatment is necessary. Treatment will prevent congenital infection in 98% of cases. The rare Jarisch–Herxheimer reaction to treatment may precipitate preterm labour. Screening in pregnancy is cost-effective, even where the disease is rare: 121 women were identified by antenatal screening in the United Kingdom from 1994 to 1997, with 18 600 tests needing to be per- formed to detect one case. Tuberculosis Mycobacterium tuberculosis infection (TB) is extremely common in the developing world. The proportion of younger people infected—including women of reproductive age—is rising, in part due to HIV infection. Pregnancy has little effect on the course of either symp- tomatic or latent TB, but the diagnosis may be delayed in pregnancy because of the nonspecific symptoms. Congenital tuberculosis is acquired transplacentally and is po- tentially fatal but extremely rare: treatment is advised principally for maternal health. Co-infection with HIV should be considered. Isoniazid, ethambutol, pyrazinamide, and rifampicin are safe in pregnancy; streptomycin can cause ototoxicity. Vitamin B6 and vitamin K supplementation are indicated. Breastfeeding is not contraindicated. Infectivity is greatly reduced

after two weeks of therapy, hence separation of mother and child is inappropriate. Protozoal infections Toxoplasmosis In the United Kingdom and North America 15–20% of adults have antibodies to Toxoplasma gondii; infection in pregnancy occurs in 0.2%. It is more common in mainland Europe and in developing countries. Infection is acquired from contact with soil, uncooked meat, or contaminated salad, and is more common in women with HIV. The condition is frequently asymptomatic, but 10–20% of mothers have lymphadenopathy or a flu-like episode. Vertical transmission occurs during pregnancy in about 30%. Transmission is lower (<10%) in early gestation, but has greater im- pact: over 75% will have clinically apparent disease. This includes the classic neonatal triad of chorioretinitis, cerebral calcification, and microcephaly. Prenatal ultrasound findings include intra- cranial calcification, cerebral ventriculomegaly (Fig. 14.16.1a), ascites, and hepatomegaly. With increasing gestation, vertical transmission increases to about 75% by term, but the risks of se- vere sequelae (Fig. 14.16.3) are less. The highest risk for congenital toxoplasmosis with a poor outcome is therefore when maternal in- fection occurs around 20–24 weeks' gestation. At this stage the risk of severe neurological sequelae is approximately 10%. Toxoplasmosis is encountered in pregnancy either as part of in- vestigations for abnormal fetal ultrasound appearances, or as a result of screening. Toxoplasmosis screening is imprecise: IgM may not be detected with proven disease, and it may also persist for months after infection. Infection is nevertheless unlikely in the previous three months if IgM is negative, or there is high-avidity IgG. Maternal in- fection is confirmed by a change from negative to positive IgG, or low to high levels of IgM. Mothers infected in pregnancy are treated with spiramycin with the aim of reducing vertical transmission, this being diagnosed or excluded using PCR on amniotic fluid taken after 18 weeks. Combination therapy of pyrimethamine and sulfadiazine with folinic acid is used if fetal infection is detected. Although re- versal of ultrasound abnormalities has been recorded after therapy, there is no consistent evidence that treatment is effective when ver- tical transmission has occurred. In the neonate, diagnosis requires IgA or IgM testing because maternal IgG will persist for up to one year. Neonatal infection is treated for one year. Because of the per- ceived effectiveness of therapy in preventing vertical transmission, screening is widely practised in Europe, but is not recommended in the United Kingdom. Malaria Plasmodium falciparum (75%), P. vivax, P. malariae, and P. ovale are transmitted by the bite of a sporozoite-bearing female anopheline mosquito. In sub-Saharan Africa, up to 8% of infant mortality is at- tributable to malaria in pregnancy, and malaria accounts for 100 000 neonatal deaths annually worldwide. Severe malarial anaemia of pregnancy causes spontaneous miscarriage, premature birth, intra- uterine growth restriction, and stillbirth. Characteristically the intervillous space is filled with fibrin. Congenital malaria from transplacental spread occurs in approximately 10% of infected preg- nancies. The newborns have fever, respiratory distress, pallor, an- aemia, hepatomegaly, jaundice, and diarrhoea. Fig 14.16.3 MRI head of a 20-day-old baby with congenital toxoplasmosis, showing severe ventriculomegaly from hydrocephalus.

 Antimalarial drugs reduce parasitaemia, placental malaria, low birth weight and, depending on their timing, perinatal death. Drugs used depend on the sensitivity of the relevant plasmodium locally and include proguanil, chloroquine, mefloquine, and artemisinin compounds. Most falciparum malaria is now resistant to mefloquine and chloroquine. Primaquine is not used in pregnancy. Treatment of malaria in pregnancy is discussed in Chapter 14.15. Artemisinin combination therapy is increasingly used for febrile malaria be- cause of resistance to other drugs and lower frequency of few side effects, although there are less safety data, particularly for the first trimester. Sulfadoxine–pyrimethamine is most commonly used as

intermittent preventive treatment, this chemoprophylaxis involving two doses at least one month apart for all pregnant women in stable transmission areas. A third dose is recommended where HIV in- fection is common. Following malaria infection, surveillance for growth restriction is advised. Trypanosomiasis Infection in pregnancy can cause miscarriage, intrauterine growth restriction, and preterm delivery. Congenital infection occurs in about 10% and may be initially asymptomatic, but jaundice, an- aemia, hepatosplenomegaly, encephalitis, and pneumonitis can then develop. Diagnosis is through placental histology, blood smear examination for parasitaemia, and enzyme-linked immuno- sorbent assay (ELISA). There is no safe and reliable treatment in pregnancy. Other conditions Notes on other infections in pregnancy are given in Table 14.16.1 FURTHER READING

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Table 14.16.1 Notes on other infections in pregnancy

Infection	Notes
Escherichia Coli	An unusual cause of chorioamnionitis and neonatal sepsis particularly of preterm neonates
Staphylococcus aureus	An unusual cause of chorioamnionitis and neonatal sepsis particularly of preterm neonates
HHV6	Transplacental transfer occurs, probably without any effect on the fetus
HPV	Vertical transmission has been reported rarely; if vaginal warts are massive they may obstruct delivery
Enteroviruses	50% have a mild respiratory or gastrointestinal illness; some have severe cramping abdominal pains simulating placental abruption that can lead to unnecessary emergency caesarean section; newborns with vertically acquired echoviral infections may have fulminant hepatic necrosis, severe coagulopathy from disseminated intravascular coagulopathy, and meningitis or myocarditis
Japanese B encephalitis virus	Particularly high mortality rates with fetal death have been reported in pregnancy
Lassa fever	Increased mortality for women in pregnancy, survival is improved by termination and ribavirin
Trichomonas vaginalis	Infections are common in pregnancy, associated with preterm delivery, can be transmitted to the newborn around birth, but there are no adverse effects on the fetus
Mycoplasma hominis	A commensal of the lower female genital tract; controversial disease role in newborns
Ureaplasma urealyticum	As for M. hominis
Lyme disease Borrelia burgdorferi	in gestation has a good prognosis if recognized early and treated aggressively; fetal death or disease, including meningoencephalitis, occurs without maternal treatment

Schistosomiasis Placental infection occurs in up to 25% in bilharzia infested areas, but there is no effect on gestational age or birth weight Candida The incidence of vaginal thrush increases with each trimester; rarely, vaginal thrush in pregnancy predisposes to congenital candidiasis

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