The Impact of Infection During Pregnancy on the Mother and Baby

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Abstract

Maternal and newborn health are strongly linked. Infection is a recognized and prominent underlying cause of both maternal and newborn pathologies. Consequently, preventive strategies and many evidence-based interventions directed toward the mother can benefit both the mother and baby. Infection continues to account for a major proportion of maternal, fetal, and neonatal mortality and morbidity worldwide. About 40 % of maternal deaths result from infection while an additional 14.5 % of maternal deaths result from abortion, often with underlying sepsis causing death. Of the three major causes of neonatal deaths (infection, prematurity, intrapartum-related deaths), infection is responsible for 28 % and preterm birth complications are responsible for 14 %. Infection is both an underlying cause of preterm birth and a major cause of complications and death in mothers and babies.

Keywords

Urinary tract infection (UTI) • Pneumonia • Bacterial vaginosis • Candidiasis • Trichomoniasis • Chlamydia • Gonorrhea • Syphilis • Tuberculosis • Group A *Streptococcus* (GAS) • Group B *Streptococcus* (GBS) • Listeriosis • Toxoplasmosis • Malaria • Parvovirus B19 • Rubella • Cytomegalovirus (CMV) • Varicella-zoster virus (VZV) • Human herpes simplex virus (HSV) • HSV-1 • HSV-2 • Human immunodeficiency virus (HIV) • HIV Type 1 (HIV-1) • HIV Type 2 (HIV-2) • Maternal infection • Neonatal infection • Perinatal infection

Maternal and newborn health are strongly linked. Infection is a recognized and prominent underlying cause of both maternal and newborn pathologies. Consequently, preventive strategies and many evidence-based interventions directed toward the mother can benefit both the mother and baby [1]. Infection continues to account for a major proportion of maternal, fetal, and neonatal mortality and morbidity worldwide. About 40 % of maternal deaths result from infection while an additional 14.5 % of maternal deaths result from abortion, often with underlying sepsis causing death [2]. Of the three major causes of neonatal deaths (infection, prematurity, intrapartum-related deaths), infection is responsible for 28 % and preterm birth complications are responsible for 14 % [2, 3]. Infection is both an underlying cause of preterm birth and a major cause of complications and death in mothers and babies.

Throughout this chapter, where treatment is discussed, expert advice should be sought in conjunction with reference to local and national guidelines.

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Urinary Tract Infection

Background

Urinary tract infections (UTIs) are the most common bacterial infections in pregnancy. Bacteriuria occurs after bacteria invade the normally sterile urinary tract. Further spread is possible. Urinary tract infections can be classified by syndrome, anatomical complication or site, or source (Table 9.1).

Epidemiology

Estimated rates of asymptomatic bacteriuria in pregnancy vary between 2.5 and 15 % [4]. Pyelonephritis complicates around 2 % of pregnancies, increasing to 25–56 % in untreated asymptomatic bacteriuria [4]. Risk factors for pyelonephritis include being black or Hispanic, being younger, having fewer years of education, nulliparity, having initiated prenatal care later, and smoking during pregnancy [5]. Additional complications of pyelonephritis in pregnancy include anemia, septicemia, acute pulmonary insufficiency, acute renal dysfunction, and spontaneous preterm birth [5].

Microbiology

Numerous organisms cause UTI in pregnancy (Table 9.2). Most infections (>90 %) involve Gram-negative rods. Gram-positive organisms (e.g., group B *Streptococcus* [GBS]) account for about 5 % of UTIs in pregnancy [6].

Pathogenesis

Several factors increase the risk of UTI in pregnancy. The normally short female urethra becomes exposed to enteric bacteria from the nearby vagina and rectum. Hygiene may be

Table 9.1 Classification of urinary tract infection

Classification		Description
Syndrome	Asymptomatic	Typically $>10^5$ organisms per mL of urine without symptoms
	Symptomatic	Typically $>10^5$ organisms per mL of urine with symptoms
Anatomical complication	Uncomplicated	Infections in healthy premenopausal women with normal structure and function of the kidneys and urinary tract
	Complicated	Infections in persons with structural or functional abnormalities of the urinary tract
Anatomical site	Lower urinary tract	Cystitis
	Upper urinary tract	Pyelonephritis
Source	Ascending infection	Infection secondary to colonization of the periurethral tissues
	Descending infection	Infection secondary to hematogenous spread

Table 9.2 Organisms implicated in urinary tract infection in pregnancy

Microscopy	Organism(s)	Microbiology
Bacteria: Gram-negative	*Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis* Other Enterobacteriaceae (e.g., *Citrobacter* spp., *Serratia* spp., *Enterobacter* spp.) *Pseudomonas* spp.	Gram-negative rods with species-specific characteristics. May be lactose fermenters (e.g., *E. coli* and *K. pneumoniae*). Some species hydrolyze urea (e.g., *Proteus* spp.) increasing urinary pH and potentially causing urinary calculi. Susceptibility profiles vary between species, with extended spectrum beta-lactamases and carbapenemases increasingly encountered
Bacteria: Gram-positive	*Enterococcus* spp. *Staphylococcus aureus* *S. saprophyticus* Other coagulase-negative *Staphylococcus* spp. *Streptococcus* spp.	Numerous species. *S. saprophyticus* commonly encountered and differentiated by novobiocin resistance. *S. aureus* is coagulase positive and may occur through hematogenous spread. Isolation of group B streptococcus, typified by a small beta-hemolytic zone and positive CAMP (Christie, Atkins, and Munch-Peterson) test, is of clinical importance
Bacteria: Acid-fast	*Mycobacterium* spp.	Includes members of the *M. tuberculosis* complex and *M. bovis*. Many mycobacteria are slow growing organisms and require specific media and incubation conditions
Fungal	*Candida* spp.	Numerous yeast species have been implicated, including *C. albicans*, *C. tropicalis*, *C. parapsilosis*, and *C. glabrata*. Microscopy reveals single or budding cells. Species may appear Gram-positive; they can be separated by biochemical testing, chrome agar, nucleic methods, or mass spectroscopy

more difficult with abdominal distension. Urinary stasis and vesicoureteral reflux occur secondary to ureteral dilation and decreased ureteral and bladder tone. Mechanical compression of the ureters and bladder from the enlarging uterus causes urinary stasis.

Clinical Features

Cystitis is associated with dysuria, urgency, frequency, and suprapubic discomfort, although the latter two symptoms also occur with advancing pregnancy. Clinical characteristics of pyelonephritis may include pyrexia, costovertebral tenderness, chills, nausea, and vomiting.

Diagnosis

Diagnosis via microscopy, culture, and sensitivity analysis permits directed therapy. Microscopy typically quantifies red cells, white cells, organisms, and epithelial cells (the latter may suggest contamination). Quantitative criteria based on the Infectious Diseases Society of America and European Society of Clinical Microbiology and Infectious Diseases have been proposed [7]:

- Acute uncomplicated UTI or cystitis in women: >10 WBC/mm^3, >10^3 colony-forming units (CFU)/mL
- Acute uncomplicated pyelonephritis: >10 WBC/mm^3, >10^4 CFU/mL
- Complicated UTI: >10 WBC/mm^3, >10^5 CFU/mL (women) or >10^4 CFU/mL (men or straight catheter urine from women)
- Asymptomatic bacteriuria: >10 WBC/mm^3, >10^5 CFU/mL in two consecutive 24-h spaced collections
- Recurrent UTI (antimicrobial prophylaxis): <10^3 CFU/mL

Treatment

Treatment regimens for UTI during pregnancy vary by location, form of infection (e.g., asymptomatic bacteriuria versus pyelonephritis), and infective agent (e.g., [7]). Antibiotics typically safe in pregnancy include amoxicillin (with or without clavulanate), cephalexin, and nitrofurantoin. Trimethoprim, a folic acid antagonist, is often avoided in the first trimester [8].

Prevention

Preventative strategies include good hygiene and postcoital voidance. Postcoital prophylaxis may be appropriate in pregnant women who suffered from frequent UTI prior to becoming pregnant [7].

Public Health Issues

Screening and treatment of asymptomatic bacteriuria during pregnancy reduce the risk of pyelonephritis [4]. Group B *Streptococcus* bacteriuria in pregnancy requires intrapartum prophylaxis to prevent early-onset GBS neonatal disease and low birthweight [9, 10].

Pneumonia

Background

Pneumonia during pregnancy is uncommon in Western countries despite reduced cell-mediated immunity, changes in respiratory physiology, and anesthetic interventions [11, 12].

Microbiology

Similar organisms cause pneumonia in pregnant and non-pregnant adults. *Streptococcus pneumoniae* and *Haemophilus influenzae* are most frequently implicated; viral causes include influenza virus (Table 9.3). The causative organism may remain undetermined despite investigation.

Epidemiology

Pregnancy does not appear to alter the incidence of pneumonia-related hospitalization (1.5 per 1,000 deliveries) [12, 13]. The incidence is considerably higher in immunocompromised human immunodeficiency virus (HIV)-infected patients, who are predisposed to *Pneumocystis jirovecii* pneumonia and bacterial pneumonia [13]. Other risk factors include anemia, asthma, immunosuppression, and possibly illicit drug use, chronic medical conditions, and smoking [12].

Pathogenesis

Host defenses (e.g., anatomical barriers, ciliary function, immune function, and phagocytic activity) prevent pathogen infiltration into the lower respiratory tract. Passage occurs when host defenses fail. Infections occur via aspiration or inhalation or hematogenously. The characteristics of the resulting infection (e.g., lobar versus multilobar, bronchial, interstitial) are a function of both host and pathogen factors.

Clinical Features

Clinical features evolve with disease progression and include dyspnea at rest, cough, fever, pleuritic chest pain, and fine rales on auscultation. Missed or delayed diagnosis can occur.

Table 9.3 Organisms frequently implicated in pneumonia during pregnancy

Organism	Infection category	Microbiology and transmission
Streptococcus pneumoniae	Bacterial	Alpha-hemolytic Gram-positive coccus typically in pairs. Bile soluble and optochin sensitive. Transmission: person to person via respiratory droplets
Haemophilus influenzae	Bacterial	Gram-negative coccobacillus. X and V factor dependent. Transmission: person to person via respiratory droplets
Staphylococcus aureus	Bacterial	Gram-positive coccus typically in clumps. Catalase and coagulase positive. Transmission: person to person by direct contact
Mycoplasma pneumoniae	Atypical bacterial	Lacks cell wall. Transmission: person to person via respiratory droplets
Chlamydophila pneumoniae	Atypical bacterial	Obligate intracellular bacterium. Previously assigned to *Chlamydia*. Transmission: person to person via respiratory secretions
Legionella spp.	Atypical bacterial	Gram-negative bacteria. Fastidious. Widespread in environment. Transmission: inhalation of aerosols containing contaminated water or dust
Influenza virus	Viral	RNA virus belonging to Orthomyxoviridae. Influenza A often associated with worse prognosis. Transmission: person to person via aerosols/secretions or via fomites
Varicella-zoster virus	Viral	DNA virus belonging to Herpesviridae. Causes chickenpox and shingles. Transmission: person to person via respiratory secretions or contact with blisters
Pneumocystis jirovecii	Fungal	Previously designated *Pneumocystis carinii*. Widespread in environment. Causes opportunistic infection in immunocompromised. Transmission: potential person-to-person spread among at-risk persons

Diagnosis

Workup typically involves correlating history and examination findings with imaging and select microbiological tests (e.g., Gram stain and sputum and blood culture). Chest computed tomography (CT) may supplement inconclusive chest X-ray (CXR) findings. Additional microbiological investigations might be required where diagnosis is difficult or a specific pathogen is suspected.

Treatment

Treatment depends on disease etiology and severity. Supportive therapies may be required. Empirical antibiotic regimens may include penicillins, cephalosporins, or macrolides. Regarding atypical infections, clarithromycin (FDA Pregnancy Category C) is less teratogenic than doxycycline (FDA Pregnancy Category D).

Prevention

Vaccination prevents many common bacterial and viral pneumonias. Pre-pregnancy counseling should include disease or vaccination history of *S. pneumoniae*, *H. influenzae* type b, influenza (inactivated vaccine), and varicella. Methods for secondary prevention include hand washing, respiratory and contact isolation, and contact prophylaxis.

Public Health Issues

Viral pneumonias, especially influenza and varicella, spread readily by aerosol in community and hospital settings. Varicella-zoster immunoglobulin (VZIG) given within 96 h of varicella exposure may prevent or attenuate disease. Although VZIG and the inactivated vaccine are considered safe in pregnancy, the live attenuated vaccine is not [13].

Bacterial Vaginosis

Background

The human vagina contains a unique bacterial microbiota. Lactic acid production by *Lactobacillus* spp. contributes to a normally acidic pH (<4.5). In bacterial vaginosis (BV), the microbiota is disrupted with increasing pH and overgrowth of vaginal anaerobes.

Microbiology

The vaginal microbiota varies with reproductive parameters including pubescence, menstruation and associated hormonal changes, pregnancy, and menopause. Typical populations are associated with characteristic ecological community state types typically dominated by *Lactobacillus* spp. Genomic sequencing has demonstrated community state types dominated by *Atopobium*, *Prevotella*, *Sneathia*, *Gardnerella*, *Ruminococcaceae*, *Parvimonas*, and *Mobiluncus* are less common in normal pregnancy [14]. Some of these organisms are associated with bacterial vaginosis [15].

Epidemiology

The most common cause of abnormal vaginal discharge in women of reproductive age is BV. Associated risks include

Table 9.4 Amsel's and Nugent's scoring systems for diagnosis of bacterial vaginosis [19, 20]

Name	Criteria		Interpretation
Amsel's	1. Thin, homogenous vaginal discharge (1 point) 2. Vaginal pH >4.5 (1 point) 3. Fishy odor released on adding alkali (1 % or 10 % KOH) (i.e., positive whiff test) (1 point) 4. Clue cells >=20 % on microscopy (1 point)		Sum criteria 1 through 4 A score of 3 or 4 indicates BV
Nugent's	1. *Lactobacillus* morphotypes		Sum criteria 1 through 3 A score of 0–3 is normal A score of 4–6 is intermediate BV A score of 7–10 indicates BV
	4+	0 points	
	3+	1 points	
	2+	2 points	
	1+	3 points	
	0	4 points	
	2. *Gardnerella* and *Bacteroides* morphotypes		
	0	0 points	
	1+	1 points	
	2+	2 points	
	3+	3 points	
	4+	4 points	
	3. Curved Gram-variable rods		
	0	0 points	
	1+ or 2+	1 points	
	3+ or 4+	2 points	

chorioamnionitis, early and late miscarriage, preterm birth, postpartum endometritis, recurrent miscarriage, and increased risk for sexually transmitted infections (STIs) including HIV (see [14]).

The estimated prevalence of BV varies widely from 4 % to 61 %, with estimates in pregnancy ranging from 6 % to 32 % [16]. Risk factors include smoking, sexual activity, douching, and black race [16]. The etiology is unknown but sexual transmission is suggested [17].

Pathogenesis

Transmissible *Lactobacillus* phages may harm the predominant (normally >95 %) commensal vaginal lactobacilli, which are replaced with a concentrated polymicrobial flora with secondary overgrowth of anaerobes [18].

Clinical Features

Features of BV include a painless homogenous clear, white or gray vaginal discharge with a distinctive fishy odor secondary to polyamines and trimethylamine. Inflammation is absent. Approximately 50 % of affected women are asymptomatic.

Diagnosis

Diagnosis is via Gram-stained vaginal smears typically scored using Nugent's criteria (often considered the gold standard) or Amsel's criteria (Table 9.4 [19, 20]).

Treatment

Oral or topical metronidazole and clindamycin are frequently recommended. Antibiotic therapy can eradicate BV during pregnancy reducing the risk of late miscarriage [15]. However, it does not reduce the risk of preterm birth or the risk of preterm prelabor rupture of membranes (ROM).

Prevention

A vaccine is not available. Risk reduction involves smoking and douching cessation, use of condoms, and reducing the number of sex partners.

Public Health Issues

Treatment in women with abnormal vaginal flora (intermediate flora or BV) may reduce the risk of preterm birth (RR 0.53; 95% CI 0.34 to 0.84; two trials, 894 women) [14].

Candidiasis

Background

Vulvovaginal candidiasis (VVC) is a common clinical problem that may present during pregnancy. Vulvovaginal candidiasis can be classified as uncomplicated or complicated, based on frequency, severity, causative agent, and host factors (Table 9.5) [21].

Table 9.5 Classification of vulvovaginal candidiasis [21]

Factor	Uncomplicated	Complicated
Frequency	Sporadic or infrequent	Recurrent (≥4 episodes per year)
Severity	Mild to moderate	Severe
Organism	More likely to be *C. albicans*	Less likely to be *C. albicans*
Host factors	Non-immunocompromised	Uncontrolled diabetic, debilitated, or immunosuppressed

Microbiology

Candida are yeasts (unicellular fungi). Normally commensal flora, *Candida* may also present as opportunistic pathogens. Numerous species are described, including *Candida albicans*, *C. tropicalis*, and *C. glabrata*. Common habitats include the skin and the gastrointestinal and genital tracts. *Candida albicans* causes approximately 80 % of yeast infections, and *C. glabrata* and *C. tropicalis* cause most of the remainder. Numerous virulence factors are documented [22].

Epidemiology

Candida infections are usually endogenous, although human-to-human transmission can occur (vertical from the mother to baby). Acquisition secondary to sexual transmission is not typical [21]. Approximately 75 % of women experience VVC once during their life; 40–45 % suffer two or more episodes [21]; 9 % of women suffer from recurrent VVC [23].

Pathogenesis

Pregnancy increases the risk of VVC because the effects of estrogen enhance *Candida* adherence to vaginal epithelial cells. Other risk factors include oral contraceptive use, broad-spectrum antibiotic use, diabetes, systemic steroids, obesity, and immunocompromised states including HIV infection [24].

Recurrent VVC can be partly attributed to reduced T-lymphocyte reactivity to *Candida* antigen, which permits proliferation and germination within the genital tract. Suspect relapse (suffered by 25–30 % of women) when culture negativity posttreatment is followed by re-isolation of an identical strain within 30 days [24].

Clinical Features

Vulvovaginal candidiasis is frequently associated with non-specific symptoms including vaginal discharge and discomfort, pruritus, external dysuria, and dyspareunia [21]. The vulva is red, often with scaling and fissures. Vaginal rugations are red and inflamed with a thick adherent vaginal discharge that is white to yellow in color and odorless [21, 24].

Candida is an uncommon cause of amnionitis [25] and neonatal skin infection at birth.

Disseminated neonatal candidiasis can involve the meninges, kidneys, and eyes. Risk factors for invasive fungal infection include prematurity, very low birthweight (LBW), central venous lines, intubation, parenteral nutrition, broad-spectrum antibiotic use, H2 blocker use, prolonged hospitalization, and colonization with *Candida* spp. [26].

Diagnosis

Diagnosis is achieved through history, examination, and microbiological investigation. Vaginal swabs should be collected for microscopy, culture, and sensitivity. Microscopic methods typically include a wet preparation and Gram stain. Methods for species level identification include growth and incubation characteristics, biochemical testing, mass spectroscopy, and nucleic acid detection.

Other causes of vaginitis should be considered in the differential, including BV, *Trichomonas vaginalis*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*.

Treatment

Various regimens have been recommended, including intravaginal imidazole therapy (e.g., topical clotrimazole) and nystatin cream [27]. Topical imidazole therapy in pregnancy may be more effective than nystatin, with 7 days of treatment required [28].

Prevention

Prevention includes broad-spectrum antibiotic avoidance, minimizing steroid use, and diabetic control. No vaccines against *C. albicans* are licensed for use [29].

Public Health Issues

A trial whose prevalent infection was candidiasis found that screening and standardized treatment for vaginal infections at 15–19 weeks' gestation reduced preterm delivery significantly [30].

Table 9.6 Complications of *Trichomonas vaginalis* infection

Complication	Cause
Premature rupture of membranes and prematurity	Reduced chorioamniotic membrane strength secondary to inflammatory response
Neonatal infection	Transmission as neonate transits the birth canal
Acute salpingitis and postpartum endometritis	Motile trichomonads cause ascending infection with associated inflammatory response
HIV transmission and infectivity	Cellular damage and altered host responses weaken defenses against co-transmission
Transmission of other secondary agents	Trichomonads may act as vehicle for other agents including bacteria, yeasts, and viruses. Some of these agents have been associated with BV
Tubal infertility and pelvic inflammatory disease	Parasites cause tubal inflammation and byproducts that harm semen with resulting infertility
Ectopic pregnancy	Tubal tissue damage secondary to inflammation may result in inappropriate implantation
Cervical cancer	Infection may cause cervical mucosal changes resulting in dysplasia or carcinoma in situ

Trichomoniasis

Background

Trichomonas vaginalis infection is one of the most commonly reported STIs globally. Originally considered a commensal, it is now recognized as responsible for numerous significant health sequelae in men and women.

Microbiology

Trichomonas vaginalis is an anaerobic, motile, flagellated protozoan that exists in several forms including infective trophozoites, amoebae, and pseudocysts.

Epidemiology

Trichomonas vaginalis is considered the most prevalent non-viral STI worldwide [31]. Rates are consistent across age groups [32]. Transmission is almost always sexual, with prevalence highest in women with multiple sex partners and a history of gonorrhea [33]. Transmission rates from infected women to men and vice versa are high, 70 % and 80–100 %, respectively [34]. Prevalence rates are approximately 10 %, depending on the population sampled. Infection may be a marker of high-risk behavior. *T. vaginalis* is commonly associated with other STIs. Most infected women have concurrent BV [35].

Pathogenesis

Symptoms develop after an incubation period of up to 28 days following sexual contact. The organism has a barbed tail (axostyle) that attaches to vaginal epithelial cells. Other virulence factors include an immunogenic surface protein (P270), cysteine proteinase secretion, and a cell-detaching factor [36]. Infection results in epithelial damage and micro-ulceration. A profound host inflammatory response can ensue. Various complications (many relating to pregnancy) have been described (Table 9.6) [34, 36–38].

Clinical Features

Only about half of infected women are symptomatic. Delayed presentation of symptoms is common with infections potentially persisting for years. Symptoms and signs include yellow or green vaginal discharge, vulvar itching, vaginal or vulvar erythema, vaginal odor, and occasionally a red erythematous cervix ("strawberry cervix") [34]. Symptomatic neonatal infection is unusual. Neonatal vaginal discharge can occur.

Diagnosis

Several diagnostic methods are available. Typically, diagnosis is via microscopic examination of a wet mount examining for motile trichomonads (sensitivity 50–60 %; specificity >90 %). Sensitivity is dependent on rapid examination, a sufficient inoculum, and an appropriate processing temperature. Culture in Diamond's media (sensitivity 85–95 %; specificity >95 %) is the traditional gold standard and tolerates a lower inoculum. However, incubation of 2–7 days is required, and cultures are prone to contamination. Although many serological techniques (e.g., complement fixation, hemagglutination) have been replaced by nucleic acid amplification testing (NAAT) (sensitivity >90 %; specificity >95 %), rapid antigen testing remains a useful diagnostic modality (sensitivity >90 %; specificity >95 %) [34, 39].

Screening for other STIs is indicated.

Treatment

Treatment for trichomoniasis typically involves nitroimidazoles such as metronidazole or tinidazole. Sex partners

require concomitant treatment irrespective of symptomatology. Nitroimidazole resistance is a continuing problem [40].

While treatment of symptomatic pregnant women is indicated, uncertainty remains regarding treatment of asymptomatic pregnant women. A Cochrane review reported that although a single dose of metronidazole may cure infection, the use of metronidazole might also increase the risk of preterm and low-birthweight babies [41]. A recent cohort study was unable to demonstrate this association [42].

Prevention

Methods of prevention include use of condoms, abstinence from sexual activity with infected individuals, and reducing partner concurrency [32, 43]. No vaccine is available.

Public Health Issues

Trichomoniasis is underdiagnosed and underreported, despite high prevalence rates and potentially serious outcomes in infected men and women. In general, problems relate to routine screening that is limited to STI clinics, vaginal wet mount preparations that are used as diagnostic standards despite limited sensitivity, and nonmandatory public health reporting.

Chlamydia

Background

Chlamydia, caused by *Chlamydia trachomatis*, is one of the most common STIs worldwide. In women, *C. trachomatis* causes genital tract infection (cervicitis), which can result in maternal and neonatal complications including conjunctivitis, nasopharyngitis, and pneumonia. *Chlamydia trachomatis* causes ocular trachoma, the most common preventable blindness due to infection. Adverse outcomes for women include pelvic inflammatory disease (PID) resulting in ectopic pregnancy and tubal infertility [44].

Microbiology

Chlamydia trachomatis (family Chlamydiaceae) is a Gram-negative bacterium that is obligately intracellular and relies on the host cell for energy given it cannot generate ATP. The species is related to *Chlamydophila psittaci* and *C. pneumoniae*.

Chlamydia trachomatis has a characteristic biphasic life cycle. The infectious form is the metabolically inert elementary body, which is transmitted in secretions. It binds to host receptors on a target epithelial cell, is phagocytosed, but then prevents phagolysosome formation. Within the cell, the elementary body transforms into a metabolically active reticulate body and replicates via binary fission in a membrane bound inclusion. After replication, reticulate bodies transform back to elementary bodies, which are released from the cell and infect another cell in the same or different host.

The various human biovars and serovars of *C. trachomatis* cause differing clinical manifestations (Table 9.7) [45].

Table 9.7 Human biovars and serovars of *Chlamydia trachomatis* [45]

Biovar	Serovar	Typical clinical manifestation
Lymphogranuloma venereum	L1, L2, L2′, L2a, L2b, L3	Invasive sexually transmitted infection
Trachoma	A, B, Ba, C	Ocular disease
	D, Da, E, F, G, H, I, Ia, J, Ja, K	Sexually transmitted infection

Epidemiology and Transmission

Chlamydia is the most common STI in the USA, with the case rate doubling between 1992 and 2012 to 456.7 per 100,000 population [46]. The disease is most prevalent in adolescents and young, sexually active women. Predictors of infection include young age, female sex, and minority race/ethnicity [35].

Transmission occurs via three mechanisms. Sexual transmission occurs in serovars associated with STI. Infection occurs less readily between females than between males or heterosexual couples. Transmission can occur via vaginal, anal, or oral sex. Vertical transmission occurs between the mother and baby during delivery. In endemic areas, the trachoma biovar is frequently spread from child to child.

Pathogenesis

In noninvasive STI, organisms infect the cervix and urethra and can then spread to the fallopian tubes. Primary infection can also occur in the rectum after anal intercourse. The target cells are the epithelial cells of the endocervix and upper genital tract. An inflammatory response ensues, with infiltration of various cell lines including neutrophils and lymphocytes. The naturally alkaline pH and exposed cervical columnar cells in adolescent women increase vulnerability to infection. The histopathology is that of granulomas and microabscess formation.

The pathogenesis of serovars causing lymphogranuloma venereum (LGV) can be characterized in three stages. In the primary stage, a painless herpetiform ulcer occurs at the site of inoculation. In the secondary stage, organisms infiltrate the lymphatic system and replicate within macrophages in regional

lymph nodes. In the tertiary stage, hyperplasia of intestinal and perirectal lymphatic tissue occurs, with abscess formation, fistulas, strictures, and potential fibrosis and granulomas.

In ocular disease, inflammation occurs secondary to infection. Infiltrates are organized into lymphoid follicles. Pannus formation occurs. Ongoing inflammation occurs with various changes including epithelial thickening and scarring, upper eyelid inversion with trichiasis, and corneal opacification.

Infections trigger a humoral response to bacterial antigens, resulting in detectable IgM, IgA, and IgG. However, natural infection may confer little protection [35].

Clinical Features

In non-LGV biovars, chlamydial infection is asymptomatic in about 75 % of women. Symptoms, when present, include vaginal discharge and dysuria typically 1–3 weeks postexposure. Signs include mucopurulent cervical discharge and hypertrophic cervical ectopy [47]. Complications include pelvic inflammatory disease (PID), infertility, ectopic pregnancy, and chronic pelvic pain. Additionally, infection increases the risk of acquiring HIV. In LGV biovars, clinical features may include a painless genital ulcer (primary stage), lymphadenitis, lymphangitis, proctitis, cervicitis, perimetritis and/or salpingitis (secondary stage), and necrosis, abscesses, fistulas, and strictures (tertiary stage).

The neonate can become infected during birth from an untreated mother, with resulting risk of conjunctivitis (30–50 %), nasopharyngitis (15–20 %), and pneumonia (5–10 %) [47].

Diagnosis

Laboratory diagnosis of *Chlamydia* is achieved using various methods including nucleic acid detection, cytology, serology, and culture. Nucleic acid methodologies are typically preferred as they have high sensitivity and specificity. Typical sample types include first void urine, endocervical swabs, and self-collected vulva-introital swabs. Historically, cytological examination was performed using a modified Giemsa stain on a smear of epithelial cell (e.g., urethral, conjunctival) scrapings and assessed for characteristic intracytoplasmic inclusions. Alternate approaches including fluorescent antibody staining are now available. Cell culture using McCoy (or HeLa) lines is possible, with diagnosis relying on staining to identify inclusion bodies. While sensitive and specific, culture is prone to contamination and is costly, complex, and time sensitive.

Serology typically relies on titer determination of IgG and IgM. IgM rises in acute infection while IgG persists. Elevated IgM and IgG endpoint titers are typically used to identify recent infection. Unfortunately, early collection may miss the antibody response, cross-reactivity can occur between species, and parallel testing with later samples may be required for interpretation. IgM antibody detection is useful in neonatal infection.

Co-infection with gonorrhea should be considered.

Treatment

Antibiotic treatment in pregnancy typically prevents transmission to the neonate [48]. Recommended regimens in pregnancy may include oral erythromycin or azithromycin or doxycycline in nonpregnant women. Test of cure may be recommended in pregnant women, although it can provide false-positive results when polymerase chain reaction (PCR) detects nucleic acid from treated but nonviable organisms [48]. Sex partners should be treated.

Prevention

Primary prevention includes personal and community sexual health education to promote future sexual risk reduction. Consistent and correct condom use effectively reduces acquisition of chlamydial infection by women and men [49].

Screening programs can reduce the incidence of PID by up to 60 % [50]. Pregnant women should be screened at their first antenatal visit, and those with multiple sex partners or aged 25 years or under should be retested in their third trimester [48].

C. trachomatis vaccine development is ongoing [51].

Public Health Issues

Chlamydial infection is largely asymptomatic and of epidemic proportions. It is the most common notifiable disease in the USA and can cause severe reproductive sequelae and costly complications: infertility, ectopic pregnancy, and neonatal disease. Clinicians play a crucial role in recognizing, screening, notifying, and treating *Chlamydia* infections.

Gonorrhea

Background

Gonorrhea is a sexually transmissible infection caused by the bacterium *Neisseria gonorrhoeae*. In women, gonorrhea is predominantly a subclinical infection and therefore not treated. Complications include upper genital tract disease

resulting in tubal infertility and increased risk of ectopic pregnancy. In pregnancy, vertical transmission can occur resulting in neonatal eye disease. In males, infection causes urethritis and epididymo-orchitis. Although uncommon, gonococcal infection can also cause disseminated disease. Concurrent infection with *Chlamydia* occurs and this is associated with similar complications. Gonorrhea enhances the sexual transmission of HIV infection [52].

Microbiology

Neisseria gonorrhoeae is a fastidious, Gram-negative diplococcus and obligate human pathogen.

Epidemiology

N. gonorrhoeae is transmitted by sexual intercourse with an infected partner, with risks of about 20 % female to male per unprotected vaginal intercourse and 50–70 % per contact for the reverse. The risk of transmission from an infected mother to her neonate is 30–47 % [53].

Pathogenesis

Primary infection of cuboidal or columnar epithelial cells is mediated by the organism attaching to the mucosal epithelium followed by penetration of organisms through and between epithelial cells within 24–48 h. A marked neutrophilic response ensues with epithelial sloughing, microabscess development, and discharge of pus. Thus incubation is brief and symptoms develop rapidly [54].

Clinical Features

In women, because gonorrhea is often asymptomatic or mildly symptomatic, it may be undiagnosed and untreated. Where present, symptoms and signs usually occur within 10 days and include vaginal discharge, dysuria, intermenstrual bleeding, and abdominal pain if ascending infection occurs with PID, with or without mucopurulent cervicitis [55]. Gonorrhea during pregnancy has been associated with pre-labor rupture of membranes (ROM) and with preterm delivery [53]. Clinical symptoms and signs are unchanged in pregnancy. However, PID is uncommon after the first trimester. Postpartum endometritis and pelvic sepsis can occur.

Neonates are infected during delivery and occasionally by ascending infection before birth, after prolonged ROM. Neonatal infection causes purulent bilateral conjunctivitis. Occasionally, infection disseminates causing sepsis, arthritis, or meningitis [53].

Diagnosis

Nucleic acid amplification tests (NAATs) are increasingly used to diagnose gonorrhea. NAATs are more sensitive and more transportable than culture [52]. However, culture and antibiotic susceptibility testing should be performed where possible as antibiotic resistance is a significant problem in *N. gonorrhoeae*. Coinfection with *Chlamydia* should be considered. Eye swabs should be collected in neonates with purulent conjunctivitis for light microscopy, culture, and sensitivity testing. In gonococcal conjunctivitis, Gram stain demonstrates intracellular Gram-negative diplococci on light microscopy.

Treatment

Antimicrobial resistance in *N. gonorrhoeae* is a significant problem. Local guidelines should be consulted. Partners should be assessed for infection and need for treatment.

Prevention

There seems to be little if any natural immunity to gonococcal infection [56]. Efforts to develop a vaccine that provides broad protection against multiple *N. gonorrhoeae* serotypes have so far been unsuccessful. Health promotion initiatives including condom use are important for disease prevention and control. Guidelines vary between jurisdictions regarding recommendations for eye drops in the neonatal period to prevent gonococcal conjunctivitis in neonates.

Public Health Issues

Public health control measures include screening of at-risk women at STI clinics and elsewhere and routine screening and treatment of patients' sex partners, testing for other common STIs, and reporting of cases by health providers to facilitate epidemiological trends and targeted control. Gonococcal antimicrobial resistance has been identified as a serious threat by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). The current treatment strategy in the UK, the USA, Europe, and

elsewhere is dual treatment with an extended spectrum cephalosporin and a macrolide. No ideal alternative has been identified and resistance has now been reported to both classes of antibiotics. Surveillance is critical to monitor antimicrobial resistance [57].

Syphilis

Background

Syphilis remains a major cause of adverse pregnancy outcome in developing countries. Congenital syphilis is a global public health problem. The WHO estimated in 2008 that 1.86 million cases of syphilis occur in pregnant women annually [58]. Untreated syphilis often results in serious long-term complications including death. Additionally, syphilis facilitates HIV transmission. Congenital syphilis can cause stillbirth, preterm birth, neonatal death, and neurodisability in survivors.

Microbiology

Syphilis is predominantly an STI caused by *Treponema pallidum* subspecies *pallidum*. Various treponemal species (and subspecies) are responsible for different disease spectra (Table 9.8). The pathogenic treponemes are unicellular, spiral-shaped organisms that demonstrate motility via periplasmic flagella. *T. pallidum* cannot be cultured on artificial media.

Epidemiology

In the USA, the rate of primary and secondary syphilis more than doubled between 2001 and 2013 to 5.3 cases per 100,000 population [59]. However, the rate in women declined to 0.9 cases per 100,000 population in 2012 [59]. Mother-to-child transmission of syphilis has declined in the USA from 10.5 to 7.8 cases per 100,000 live births since 2008, reflecting the reduction in syphilis in women [50].

Table 9.8 *Treponema*

Treponeme	Disease
Treponema pallidum ssp. *pallidum*	Syphilis
Treponema pallidum ssp. *pertenue*	Yaws
Treponema pallidum ssp. *endemicum*	Bejel
Treponema carateum	Pinta
Nonpathogenic treponemes	Normal oral microbiota

Transmission is largely due to sexual intercourse. Transmission of infection to the fetus is vertical from an infected mother by either hematogenous spread or direct contact with infectious genital lesions. The likelihood of fetal infection is nearly 100 % if the mother has early syphilis characterized by spirochetemia (identified by rapid plasma reagent [RPR] >= 1:8) and up to 70 % 4 years after the acquisition of maternal disease [60, 61]. Seroprevalence is generally low in high-income countries.

Pathogenesis

Infection occurs after *T. pallidum* penetrates intact mucosa or enters via abraded skin. Rapid spirochetemia ensues with organ invasion and a central nervous system (CNS) tropism. The median incubation period is 21 days depending on inoculum size (range 3–90 days). An intense host immune response ensues with resulting inflammation defining clinical expression.

Untreated syphilis passes through three disease stages: primary, secondary, and tertiary. The primary stage is characterized by the chancre, a painless ulcer at the site of inoculation that heals weeks to months later. Regional lymphadenopathy can occur. The secondary stage occurs approximately 2 months after the chancre heals. It is typified by constitutional symptoms, a characteristic maculopapular rash, condylomata lata, and generalized lymphadenopathy. Other manifestations may occur (e.g., ophthalmic, gastrointestinal, hepatic, nervous system, etc.). A proportion of untreated patients progress to tertiary syphilis characterized by an obliterative endarteritis and cardiovascular disease, symptomatic or asymptomatic neurosyphilis, and/or gummatous disease characterized by widespread granulomatous lesions.

Primary and secondary stages are highly contagious. Transplacental infection can occur at any stage of pregnancy.

Clinical Features

Syphilis has protean clinical manifestations, particularly during the secondary and tertiary stages. Over half of infected infants are asymptomatic at birth or have nonspecific signs. Overall, 15 % of infants of mothers with untreated syphilis have clinical evidence of congenital syphilis [62]. Consequently, infections should be suspected when maternal serology is reactive, especially in the context of nil or inadequate treatment.

Women with untreated syphilis experience 21 % higher rates of fetal loss and stillbirth, 9.3 % higher rates of neonatal death, and 5.8 % higher rates of prematurity or low birthweight

(LBW) [62]. Other congenital features can include hepatomegaly with or without splenomegaly, a generalized vesicular, bullous skin rash initially with mucus patches that then slough (40 %), and bone changes of osteochondritis on X-ray (75–100 %), although none are pathognomonic [63].

Diagnosis

Various testing methodologies are utilized in the diagnosis of congenital syphilis, as reviewed elsewhere [64, 65]. A summary follows, although expert advice is recommended for test selection and interpretation:

- *Microscopy*. Dark field microscopy is used to observe motile spirochetes. Antigen detection is also possible by direct fluorescent antibody (DFA-TP).
- *Culture*. Not available in vitro.
- *Nucleic acid detection*. Various mono- and multiplex assays have been developed for identifying *T. pallidum* directly from clinical material.
- *Serology*. Serological testing is the mainstay of laboratory diagnosis and relies on treponemal and nontreponemal tests. Nontreponemal tests include the RPR test and Venereal Diseases Research Laboratory (VDRL) test. These tests detect anticardiolipin antibodies produced during active syphilis, although these antibodies are nonspecific and yield false positives with pregnancy or other diseases. Diagnosis consequently requires confirmation with treponema specific tests. The nontreponemal tests, which are performed in both qualitative and quantitative formats, are useful for identifying active infection (or reinfection) and monitoring treatment efficacy. Treponemal tests (e.g., fluorescent treponemal antibody absorption test [FTA-ABS], hemagglutination assay [TPHA]) target treponema specific antibodies. Unlike nontreponemal antibodies, these tests retain sensitivity during treatment and latent syphilis, although consequently they are not useful for detecting reinfection or treatment response.

Various point-of-care assays have been developed [66], requiring whole blood, serum, or plasma. Such tests may be well suited to developing countries given their minimal equipment and training requirements and rapid turnaround time (10–20 min). Sensitivity and specificity vary with assay and operator, and such assays are not licensed for use in all countries.

Diagnostic confirmation of congenital syphilis in the neonate is complicated by both passive transfer of maternal immunoglobulin (IgG) and by a delay in the production (and therefore detection) of IgM antibodies (which do not cross the placenta). Therefore, congenital syphilis cannot be excluded by negative tests. Any increased RPR titer compared to the mother is suspicious. Clinical assessment frequently involves lumbar puncture with cerebrospinal fluid (CSF) assessment and radiography. Performing such investigations in asymptomatic infants especially in resource-poor settings is unsurprisingly problematic.

It is typically recommended that pregnant women be screened at their first antenatal visit and again during the course of their pregnancy if considered at risk [21].

Treatment

T. pallidum remains susceptible to penicillin; the drug is used for treating maternal infection and fetal infection and preventing maternofetal transmission. Timely treatment of active syphilis in pregnancy reduces adverse syphilis-related pregnancy outcomes [67]. The route, formulation, and duration selected for treatment depend on various factors including stage and clinical manifestation [21]. Treatment decisions are based on identifying syphilis in the mother, confirming the adequacy of maternal treatment, identifying evidence of syphilis in the infant, and comparing maternal RPR or VDRL titers at delivery with those of the infant.

Prevention

Primary prevention includes programs promoting safe sex including consistent, correct condom use, which reduces acquisition of syphilis by men and women [49]. No vaccine is available.

Secondary prevention depends on screening programs for syphilis in pregnancy that typically emphasize access to antenatal care early in pregnancy, decentralized services that provide rapid simple test results with appropriate treatment, partner notification and repeat testing in pregnancy, opportunistic testing at sites other than antenatal clinics, and combining programs for prevention of vertical transmission of HIV with that of syphilis [68].

Congenital syphilis can be prevented by detection of maternal infection by the second trimester and appropriate maternal treatment with penicillin.

Public Health Issues

Syphilis, both maternal and congenital, remains a major public health problem worldwide. Screening programs in pregnancy are justified and cost-effective even in low-prevalence areas. Antenatal syphilis screening interventions could halve the incidence of stillbirth and perinatal death caused by syphilis [69] but there are barriers to achieving this, especially in low-income countries.

Tuberculosis

Background

Although documented since antiquity, tuberculosis (TB) probably became epidemic with high mortality in the industrialized world of the seventeenth and eighteenth centuries. The discovery of streptomycin and then isoniazid after World War II permitted treatment and cure. However, from the mid-1980s the HIV epidemic has reversed the decline in TB incidence with extensive co-infection. Although pregnancy does not change the course of TB, it presents risks to both the mother and fetus [70].

Microbiology

Mycobacterium tuberculosis (family Mycobacteriaceae) most commonly causes TB, although other *M. tuberculosis* complex (MTC) members (*M. africanum*, *M. bovis*, *M. canetti*, and *M. microti*) also cause disease. The MTC comprises obligate aerobic, nonmotile, non-spore-forming acid-fast bacilli typified by slow growth in solid media (3–8 weeks) compared with liquid broth media (1–3 weeks). Acid-fast stain is used rather than Gram stain given the high mycolic acid content of the cell wall.

Epidemiology and Transmission

Humans comprise the sole reservoir for *M. tuberculosis*. In 2012, approximately 8.6 million people developed TB, with 1.3 million deaths [71].

Transmission is via respiratory droplets, which can remain airborne for hours and penetrate into the alveoli due to their small particle size [72]. Pregnancy does not alter the risk of transmission. Patients with smear-positive disease are more infectious than those with smear-negative culture-positive pulmonary disease; those with culture-negative pulmonary disease and extrapulmonary TB are noninfectious [70].

Active disease, uncontained by cell-mediated immunity, is most common in immunosuppressed HIV patients and children younger than 5 years of age [72]. In infected women, the incidence of TB peaks at 25–34 years [70].

Pathogenesis

After droplets containing *M. tuberculosis* access the terminal airspaces, activated macrophages ingest the bacilli that multiply causing cell lysis. Infection either remains contained at the site of the primary lesion (the Ghon focus) and draining regional lymph nodes or active disease occurs in the lung or spreads hematogenously to the CNS (meningitis with or without tuberculomas), bones or joints (most commonly the spine [Pott's disease]), genitourinary system (potentially causing infertility), lymph nodes, pleura, and peritoneum. Cell-mediated immunity appears 3–8 weeks after infection.

Clinical Features

In healthy adults infected with TB, 90–95 % have persistent, asymptomatic, latent TB, and only 5–10 % develop active TB [73]. The most common type of TB is pulmonary disease, although 5–10 % of pregnant women have extrapulmonary TB [70]. Risk factors include HIV, malnutrition, poorly controlled diabetes, and malignant disease. Clinical features include a persistent cough of longer than 2 weeks, fever, night sweats, weight loss, dyspnea, hemoptysis, chest pain, and malaise.

Diagnosis may be delayed in pregnant women due to nonspecific symptoms that mimic those of pregnancy [see 74], and the rate appears to significantly increase postpartum [75]. Infection during pregnancy (which may be compounded by concomitant HIV infection) may result in acute fetal distress, prematurity, LBW, and increased risk of abortion [76].

Congenital infection is rare and due to hematogenous spread via the umbilical vein or ingestion from infected amniotic fluid [73]. Infection more commonly occurs after birth via horizontal transmission from infective family members. Neonatal manifestations may mimic bacterial or viral infections that are unresponsive to usual treatment. The most common presentation is with hepatosplenomegaly (76 %), respiratory distress (72 %), fever (48 %), and lymphadenopathy (38 %) [72].

Diagnosis

Numerous modalities are available for the diagnosis of *Mycobacterium* [77]. Mantoux testing, considered safe in pregnancy, involves the intradermal administration of tuberculin purified protein derivative to assess cell-mediated immunity. Patient risk factors are interpreted against zone size to categorize positive or negative interpretations. Positive Mantoux tests are further evaluated with CXR, although such testing may be delayed in pregnancy. False-positive results may occur after Bacillus Calmette-Guérin (BCG) vaccination. False-negative results may occur for several months in congenital TB [70] or in the immunocompromised.

Laboratory-based investigations include direct sputum smears, culture, and NAATs. Direct sputum smears collected on three consecutive mornings are assessed using microscopy and culture. Methods of staining include Ziehl-Neelsen (ZN) and fluorescent staining.

Culture is required for definitive diagnosis and drug susceptibility testing. Unfortunately, not all infections are culture

positive. Specimen decontamination may be required prior to culture to prevent overgrowth by non-mycobacterial species. Growth is typically slow, requiring several weeks. In suspected culture-negative cases, nucleic acid detection methods may be beneficial, although sensitivity is substantially greater in smear-positive versus smear-negative patients [78].

Treatment

Considerations regarding treatment include whether the patient is Mantoux positive alone (i.e., infection without evidence of active disease), whether active disease is present, and whether the patient is HIV infected or has other risk factors.

Treatment principles that aim to eradicate TB, ensure fewer relapses/failures, achieve higher cure rates, and reduce resistance, include [79, 80]:

- Use of multiple drugs to which *M. tuberculosis* is sensitive
- Appropriate drug combinations for a sufficient period of time
- Use of directly observed therapy strategy (DOTS) wherever possible
- Use of in vitro drug susceptibility and local resistance patterns to guide initial drug choices
- Adding multiple not single drugs to a failing regimen
- Emphasizing completion of courses and monitoring reasons why therapy is not completed

Medications include (but are not limited to) isoniazid, pyridoxine, rifampicin, and ethambutol [81]. Certain antituberculous drugs (e.g., streptomycin, amikacin) are considered harmful to the fetus (US Food and Drug Administration [FDA] Pregnancy Category D).

Prevention

Prevention of TB in mothers and children remains a challenge. Potential methods in children include minimizing exposure to infectious sources, provision of BCG vaccine to non-HIV-infected children, and provision of isoniazid preventive therapy to exposed children less than 5 years of age [82]. Methods proposed in pregnancy include isoniazid preventive therapy in patients with concurrent HIV infection or at risk of progression of latent TB [82].

Public Health Issues

The Stop TB Strategy is a six-point framework devised by the WHO to reduce the global burden of TB [83].

Group A Streptococcus

Background

Streptococcus pyogenes (Group A *Streptococcus*, GAS) is an important pathogen causing puerperal sepsis, a disease associated with significant morbidity and mortality in both the mother and baby. Other diseases caused by GAS include pharyngitis, impetigo, rheumatic fever, postinfectious acute glomerulonephritis, and necrotizing fasciitis. Together, GAS, GBS, group C *Streptococcus* (GCS), and group G *Streptococcus* (GGS) comprise the so-called pyogenic streptococci [84].

Microbiology

Streptococcus pyogenes (family Streptococcaceae) is a Gram-positive coccus. The species is facultatively anaerobic, beta-hemolytic, catalase negative, and typically encapsulated. The name GAS is derived from Lancefield's method of grouping based on cell-wall carbohydrate composition, and this provides a way of differentiating the species from other beta-hemolytic species. The organism can be further serotyped using M protein, which is an antiphagocytic virulence factor that interferes with the complement cascade. Certain M strains (e.g., M1 and M28) may be more virulent [85]. In addition to M protein, the organism expresses numerous other virulence factors, described as being somatic, extracellular, or constituting pyrogenic superantigens [86].

Epidemiology

Puerperal fever is most prevalent in the developing world (≥75,000 maternal deaths per year) with lower rates in high-income countries such as the USA and Australia [87]. Group A *Streptococcus* is a principal cause of puerperal sepsis. Although 50 % of cases occur in the first 2 days postpartum, some cases can occur after 1 week, or prepartum [88]. Rates of maternal and fetal mortality are probably greatest in prenatal infection (56 % and 71 %, respectively), followed by early and then late infection [88]. The overall carriage rate of GAS is estimated between 0.03 % and 0.06 % in pregnancy [89]. While infection rates of 3 % are expected when a patient is colonized, actual infection rates in the USA stand at 6 per 100,000 [90]. The discrepancy in these values may be due to innate or acquired immunity or due to host genetics [91].

Transmission

Transmission is normally person to person via contact or droplet spread. Organisms can also survive in contaminated food or fomites [92].

Pathogenesis

Mechanisms of infection can be categorized into endogenous versus exogenous infections, nosocomial versus community-acquired infections, and early versus late infections. The initial focus of infection varies (e.g., urogenital tract, surgical incisions, or breast tissue). Post vaginal delivery, endogenous bacteria can invade the disrupted birth canal before seeding hematogenously. Similarly, during cesarean section, both endogenous and exogenous floras can be surgically implanted. After the organism enters the bloodstream, numerous virulence factors contribute to poor prognosis, including exotoxins (e.g., streptolysin O, streptolysin S), connective tissue invasion (e.g., hyaluronidase), complement system disruption (e.g., C5a peptidase), DNase production, neutrophil disruption (e.g., *Streptococcus* chemokine protease), and fibrin digestion (e.g., streptokinase).

Clinical Features

The initial diagnosis of puerperal sepsis may be difficult given the disease is uncommon and the symptoms nonspecific. Additionally, fever and pain may be masked by postpartum pain and analgesia use. Red flag signs include pyrexia, sustained tachycardia, tachypnea, abdominal or chest pain, diarrhea or vomiting, and uterine or renal angle tenderness [93].

Diagnosis

Diagnosis is primarily via microscopy and culture. Nucleic acid testing and serological methods may also be useful. Diagnostic workup typically includes blood cultures and endocervical, high vaginal, and/or perineal swabs. Midstream urine collections should also be performed. The organism is suspected when culture reveals a facultative anaerobic Gram-positive coccus that is catalase negative and beta-hemolytic. Confirmatory methods may include Lancefield latex agglutination testing, PYR testing (although this is also positive in group D organisms), mass spectrometry, and nucleic acid testing. M-typing may be warranted in cluster analysis. Serological tests include antistreptolysin O titer (ASO) and antideoxyribonuclease-B titer (anti-DNase B).

Treatment

Patients with suspected puerperal fever require immediate investigation and treatment. Such pathways may include clinical assessment, vital sign monitoring, fluid resuscitation, oxygen, antibiotics, and ICU admission (e.g., [94]). Given GAS remains sensitive to penicillin, benzylpenicillin typically forms the mainstay of treatment. The addition of a clindamycin has been recommended for a number of reasons including toxin suppression, lack of inoculum effect, inhibition of M-protein synthesis, suppression of penicillin binding protein synthesis, a long post-antibiotic effect, and immune modulation [95]. Surgical intervention may be required for source control. Decolonization of pregnant women with known GAS-positive status has been suggested prior to delivery [88].

Prevention

Prevention of perinatal GAS infection requires rigorous infection control policies to limit the possibility of nosocomial infection. For example, appropriate hygiene should be practiced during delivery and surgical instrumentation should be sterile before use. Pregnant women should maintain good hygiene including washing hands. Health-care providers should educate women on the symptoms of infection and be alert to the emergence of clusters. No vaccine is presently available.

Public Health

Acquisition of GAS occurs in both community and nosocomial settings. Asymptomatic carriage occurs in 5–30 % of the population [96]. Nosocomial clusters have occurred through an affected health-care worker [97]. Although invasive GAS infection is not notifiable in all jurisdictions, it is recommended that public health units be notified especially in the context of clustered cases (e.g., [98]). The duration of infectivity depends on the site of infection (e.g., throat versus skin lesions) and whether appropriate antibiotic treatment has been provided [99].

Group B Streptococcus

Background

Streptococcus agalactiae (GBS) was recognized as a major cause of bovine mastitis in the 1930s and emerged as a neonatal human pathogen in the late 1960s. Phylogenetic analysis of multilocus sequencing type data demonstrates common ancestry between bovine and human GBS [100]. Preventative strategies, based on intrapartum chemoprophylaxis for maternal carriers in Australia, North America, and some countries in Western Europe, have led to up to 80–90 % reduction in early-onset (<48 h of life) GBS disease (EOGBSD) though such intervention has not been recommended in a recent Cochrane systematic review [101].

Microbiology

Streptococcus agalactiae is a Gram-positive coccus that forms chains when grown in broth media and exhibits beta-hemolysis on blood agar. Defined as Lancefield group B based on its carbohydrate cell surface antigens, the organism is known as group B beta-hemolytic *Streptococcus*. Virulence factors include its polysaccharide capsule, capsular sialic acid residues, lipoteichoic acid, and deacylated glycerol teichoic acids. Five capsular polysaccharide types cause >85 % invasive disease: Ia, Ib, II, III, and V [9, 102].

Epidemiology

The reservoir in humans is the gut. The organism colonizes the lower genital tract of 5–40 % of women, with 50–75 % of their newborns becoming colonized, although only ~2 % acquire EOGBSD. Variance in maternal carriage is due to demographic, endocrine, and behavioral factors, in addition to site swabbed and microbiological methodology [100, 103, 104]. Transmission is not sexually acquired. Neonatal infection can be early onset (≤ 48 h) or late onset (> 48 h and up to 3 months of age); EOGBSD is the most common cause of early-onset neonatal infection in the developed world. Neonatal infection manifests as pneumonia, bacteremia, and less commonly meningitis.

The global burden of EOGBSD for infants in largely developed countries with antibiotic prophylaxis is estimated at 0.43 per 1000 live births (95 % CI, 0.37–0.49); the incidence and case fatality are twice those of late-onset GBS disease (LOGBSD) [102].

Risk factors that have very high attack rates (>50/1000 live births) but are relatively uncommon include GBS bacteriuria and a sibling with EOGBSD. Risk factors with lower attack rates (10–25/1000 live births) but more prevalent include heavy vaginal culture at delivery, preterm birth, prolonged ROM, and intrapartum fever [105]. Recent publications provide risk assessment based on maternal factors for neonatal sepsis including antibiotic prophylaxis [106].

Pathogenesis

Neonatal GBS infection is most commonly caused by ascending infection via the amniotic fluid. Infected amniotic fluid interfaces with the fetal lungs causing fetal infection and may initiate preterm labor. Less commonly, colonization occurs during delivery, with subsequent infection transmitted via either maternal or nosocomial routes. Neonatal infection is related to the absence of maternal type-specific IgG antibodies [107]. The pathogenesis of LOGBSD is less well understood and is thought to be due to persistence of oropharyngeal colonization with development of invasive infection or nosocomial transmission of infection. Breast milk transmission of GBS does occur in LOGBSD [108]. Maternal febrile morbidity occurs in 21 % of untreated carriers [109].

Clinical Features

Maternal carriers are usually asymptomatic but may develop clinical chorioamnionitis with or without ruptured membranes or a UTI. EOGBSD most commonly presents with respiratory distress or apnea in the term infant, and presentation may be protean in the preterm infant [103].

Diagnosis

Maternal carriage is diagnosed by culturing a low vaginal swab on selective media. Colony morphology and Gram stains permit presumptive identification of GBS, with definitive identification achieved through Lancefield grouping, additional biochemistry, mass spectrometry, and/or nucleic acid testing. Selective media can be used to culture rectovaginal swabs.

A rapid method of GBS detection is PCR at onset of labor. Analysis suggests that it is a cost-effective, accurate, and effective method to determine intrapartum chemoprophylaxis [110].

Neonatal EOGBSD is diagnosed by culturing blood and CSF. CXR may be consistent with infection. The diagnosis is supported by a positive urine streptococcal antigen, abnormal white cell count, elevated C reactive protein, or proinflammatory cytokines.

Treatment

Maternal chorioamnionitis is typically treated with parenteral penicillin and gentamicin or alternative antibiotics if the mother is allergic. Neonates with EOGBSD are treated with penicillin. In the event of allergy, alternative antibiotics include cephalosporins, vancomycin, or clindamycin, although resistance is increasing to clindamycin [9].

Prevention

The CDC recommends universal screening at 35–37 weeks' gestation [9]. Evaluation of a universal screening approach significantly reduced EOGBSD by >85 %, whether performed at 28 weeks' [111] or 35–37 weeks' gestation [112]. The decline reported was to 0.22 and 0.37 per 1000 live

births, respectively. In 2010, the US rate was reported as 0.26 cases per 1000 live births [113].

Capsular, polysaccharide-protein conjugate, GBS vaccines have been developed, although none are licensed for use. Significant protective IgG titers in the mother provide passive protection by transplacental transfer. Phase II clinical trials are under way for a candidate GBS trivalent (Ia, Ib, III) vaccine in pregnant women [107].

Public Health Issues

Intrapartum chemoprophylaxis for maternal GBS carriers has been very successful in reducing EOGBSD. The most effective prevention is likely to be an adolescent or maternal vaccine [107, 114, 115], which would prevent stillbirth, preterm birth, EOGBSD, and LOGBSD.

Listeriosis

Background

Listeriosis is caused by *Listeria monocytogenes*. Although listeriosis is uncommon, its incidence increases in pregnancy. Most cases in pregnancy are sporadic with occasional outbreaks traced to a common source. Contaminated food is typically implicated. Adverse outcomes in pregnancy include miscarriage, stillbirth, chorioamnionitis, preterm delivery, and neonatal infection. The last can be divided into early-onset sepsis (caused by vertical ascending or hematogenous transmission) or late-onset meningitis (due to nosocomial infection) [116].

Microbiology

Listeria monocytogenes (family Listeriaceae) is a facultative anaerobic motile Gram-positive rod. The organism is characterized by tumbling motility at 25 °C caused by peritrichous flagella, which do not develop at 37 °C. It reproduces at low temperatures, permitting replication in refrigerated goods. Thirteen serotypes of *L. monocytogenes* cause human disease. Serotypes 1/2a, 1/2b, and 4b cause the greatest burden of disease [117], with the last frequently implicated in late-onset sepsis. Of six species, only *L. monocytogenes* is pathogenic for humans.

Epidemiology

The organism is commonly found in soil, dust, processed food, produce, the gut, and feces of domestic and wild animals as well as the human gastrointestinal tract (70 % healthy people and up to 44 % pregnant women), although positive vaginal swabs are rare, except with perinatal listeriosis. About one in seven (14 %) cases of *Listeria* infection occurs during pregnancy [118]. Additionally, individuals with decreased immune function or aged 65 years and over are at increased risk of infection. Pregnant women are about ten times more likely to suffer *Listeria* infection than the general population [118].

Pathogenesis

Listeria monocytogenes possesses multiple virulence factors that contribute to its pathogenesis [see 119, 120]. After the organism is ingested, it transits into the bloodstream. It evades the humoral immune system by internalizing itself in phagocytic cells. Once internalized, it escapes the vacuole using listeriolysin O. It then spreads between cells via expression of ActA and positive regulatory factor A (prfA). The organism has tropism for the CNS and placenta. Ascending infection may also occur secondary to maternal vaginal colonization. Incubation varies between 11 and 70 days (mean 31 days) [116, 121].

Clinical Features

Common maternal manifestations, identified in 222 patients with perinatal listeriosis, included fever of >38 °C (65 %), flu-like illness 34 %), being asymptomatic (31 %), leukocytosis and positive blood culture (43 %) or amniotic fluid culture (8 %), and cervical/vaginal culture (34 %) or placental culture (11 %). Serious maternal illness rarely occurs [122]. Miscarriage or stillbirth occurred in 20 %, and 68 % of neonates were infected. The most common neonatal manifestations of early listeriosis were respiratory distress (60 %), fever >38 °C (48 %), and neurological signs with meningitis (25 %) [122].

Diagnosis

Diagnosis is reliant on suspecting listeriosis in pregnant women with fever or flu-like illness. Diagnosis is typically via microscopy and culture. Key characteristics include the regularly shaped Gram-positive rods that demonstrate tumbling motility in wet mounts or via the hanging drop technique. Phenotypic methods available for differentiation of members of *Listeria* include beta-hemolysis, hippurate hydrolysis, CAMP testing, and carbohydrate utilization. Identification can also be achieved through automated identification systems or mass spectrometry. Nucleic acid tests

are available particularly for environmental and food samples. Typing can be performed through serological means or via nucleic acid testing.

Treatment

Ampicillin is generally considered the treatment of choice. It is important to note that because the organism internalizes within cells, antibiotics that test sensitive in vitro (e.g., aminoglycosides) may fail in vivo.

Prevention

Pregnant women are advised to avoid foods including soft cheeses, unpasteurized milk, raw fish, and refrigerated preprepared foods including delicatessen meats, pâtés, and salads. Raw foods should be washed or peeled to remove soil. National guidelines have been prepared for the food industry [123]. Hand washing is important. There is no vaccine.

Public Health Issues

Listeriosis is an important public health problem and both sporadic cases and outbreaks of listeriosis occur after ingestion of contaminated food. The incubation period is highly variable (1 to >90 days). Listeriosis is a notifiable disease in the USA and public health investigations follow case notifications. Risk is reduced by appropriate food preparation, consumption, and storage; control measures must address the entire farm-to-fork continuum [124].

Toxoplasmosis

Background

Toxoplasma gondii is a zoonotic protozoan organism associated with cats. Although toxoplasmosis acquired during pregnancy is often asymptomatic in the mother, vertical transmission to the fetus results in congenital toxoplasmosis or sequelae at various times after birth.

Microbiology

Toxoplasma gondii is an obligate intracellular protozoan. The organism has a sexual stage in cats and an asexual stage that can occur in other animals, including humans. The life cycle begins when a cat (the definitive host) ingests a tissue cyst initiating the sexual stage. The cat then passes unsporulated fecal oocysts, which sporulate and contaminate soil, feed, or water sources and are ingested by intermediate hosts (e.g., birds and mammals including humans). After ingestion, the oocyst transforms into a tachyzoite that localizes to neural or muscle tissue before forming tissue cysts. If tissue-containing cysts are further ingested by a cat, the life cycle restarts. Alternatively, humans can again consume the cyst-containing tissue, resulting in transmission. In cases where the intermediate host is a pregnant woman, vertical transmission to the fetus can occur.

Epidemiology

Although toxoplasmosis occurs worldwide, rates vary within and between countries. In the USA, rates of toxoplasmosis have declined in locally born individuals aged between 12 and 49 years from 14.1 % in 1988–1994 to 6.7 % in 2009–2010 [125]. The global incidence of congenital toxoplasmosis is 1.5 per 1000 live births, but rates vary between countries. Incidence depends on primary infection in pregnancy, gestational age at acquisition, and prevention/detection programs. Vertical transmission increases throughout pregnancy, from 6 % at 13 weeks' to 40 % at 26 weeks' and 72 % at 36 weeks' gestation, with less severe consequences to the fetus the later the occurrence of congenital infection [126]. The risk of developing early signs such as chorioretinitis and hydrocephaly is greatest (~10 %) when seroconversion occurs at between 24 and 30 weeks' gestation [126].

Pathogenesis

Human, and thus maternal, infection occurs via four principal mechanisms (Table 9.9).

Congenital toxoplasmosis results from transplacental passage of tachyzoites to the fetus [127]. After maternal transmission, the organism is released from cells resulting in a parasitemia that disseminates to virtually all cells and tissues. Primary maternal infection is associated with parasitemia with a delayed humoral and cellular response as immunity develops. This phenomenon, when combined with the increasing placental blood flow associated with advancing pregnancy, explains the greater risk of transmission as pregnancy advances [128].

Table 9.9 Transmission of *Toxoplasma gondii*

#	Mechanism	Associated factors
1	Ingestion of tissue cysts	Consumption of raw or undercooked meat
2	Ingestion of oocysts	Ingestion of soil, contaminated water, unwashed vegetables, or cat feces
3	Mother to fetus	Pregnancy
4	Iatrogenic	Transfusion with infected blood products

Table 9.10 Interpretation of *Toxoplasma gondii* serology

	Interpretation
IgM, IgA	Appear within several days of infection and remains detectable for months to years *Maternal*: detection during pregnancy may indicate whether acute or past infection *Pediatric*: detection after birth likely indicates congenital infection given IgM and IgA do not cross the placenta
IgG	Appears 1–2 weeks after infection and remains elevated *Maternal*: absence in the presence of IgM may indicate acute infection but requires repeat testing to identify seroconversion. Acute infection may be assessed by avidity testing or a fourfold rise in titer comparing acute and convalescent titers *Pediatric*: IgG crosses the placenta limiting interpretation of disease state

Clinical Features

Over 90 % of primary infections in immunocompetent pregnant mothers are asymptomatic. When symptomatic, complaints include headache, malaise, and cervical lymphadenopathy. While congenital toxoplasmosis is not initially apparent in about 85 % of neonates, chorioretinal and neurological abnormalities develop later. Signs at birth range from mild chorioretinitis to severe early presentation with microcephaly, hydrocephalus, and seizures [127].

Diagnosis

Diagnosis of toxoplasmosis can be difficult given patients are often asymptomatic. Serological diagnosis is typically through the interpretation of IgM, IgG, and IgA (Table 9.10). Serological testing typically results in three possibilities:

1. Recently acquired maternal infection with a fetus at risk of congenital disease (e.g., IgM positive, with or without low avidity IgG, or IgG with increasing titer)
2. Maternal infection acquired before pregnancy with an almost zero risk to the fetus of congenital disease unless the mother is immunocompromised (e.g., low avidity IgG or non-rising IgG titers, in the presence or absence of IgM)
3. Equivocal results requiring repeat testing

Alternative methods of diagnosis include nucleic acid testing from tissue or fluid (e.g., amniotic fluid at 18 weeks) and imaging including ultrasound assessment of calcification or hydrocephalus [129]. The organism can also be detected directly in stained tissue or fluid samples.

Treatment

CDC recommendations for acutely infected pregnant women in the first trimester or early second trimester include spiramycin and pyrimethamine/sulfadiazine and leucovorin during the late second trimester and third trimester [130]. The benefit of treatment during pregnancy remains uncertain [131]. Pyrimethamine, sulfadiazine, and leucovorin have been recommended in the treatment of congenitally infected newborns [132].

Prevention

Women should be educated at their first antenatal visit regarding the risk of toxoplasmosis from eating undercooked meat, from exposure to cat feces, and through soilborne transmission. Hand washing is important after handling raw meat, cat feces, and soil.

Screening for *T. gondii* primary infection during pregnancy remains controversial for reasons such as cost, identification of risk factors, the availability of appropriate tests, the low sensitivity of screening due to false-positive results, and questions regarding the effectiveness of treatment during gestation [133]. Routine screening is recommended in some countries (e.g., France) where prevalence is high.

Public Health Issues

Health-care providers are central to implementing primary prevention. Governments and the meat industry need to continue efforts to reduce *T. gondii* in meat [134]. Primary prevention is typically through education of pregnant women regarding sources of infection [135]. While some countries (e.g., France, Austria) undertake secondary prevention through prenatal or neonatal screening, evidence regarding the effectiveness of prenatal treatment is lacking [135].

Malaria

Background

Malaria is a cause of significant maternal and neonatal morbidity and mortality. Maternal outcomes during pregnancy include anemia, cerebral malaria, severe disease, and a risk of mortality [136]. Fetal and post-birth outcomes are wide ranging, depending on the stage of pregnancy, and include miscarriage, stillbirth, intrauterine growth restriction (IUGR), preterm delivery with LBW, neonatal mortality, congenital malaria, anemia, and increased risk of mortality before 5 years of age [136].

Epidemiology

Malaria occurs in most tropical regions of sub-Saharan Africa, Southeast Asia, and Latin America. Five species of *Plasmodium* infect humans: *P. falciparum*, *P. vivax*, *P. ovale*,

P. malariae, and *P. knowlesi*. *P. falciparum* is typically associated with the greatest mortality followed by *P. vivax*. *P. falciparum* is prevalent in sub-Saharan Africa, while *P. vivax* is widely distributed in Southeast Asia and South America.

Around 1.2 billion individuals were at high risk (>1 case per 1000 population) of malaria in 2012 [137]. In 2010, malaria caused an estimated 1.24 million deaths, with 714,000 deaths occurring in children younger than 5 years [138]. Malaria is more common in pregnancy; approximately 50 million pregnancies and over 40 % of births occur in endemic malarial areas of the tropics and subtropics [139]. The risk of adverse outcome is greater in first pregnancies and HIV-infected pregnant women [136].

Microbiology

Malaria is caused by infection with intracellular protozoan parasite of the genus *Plasmodium*. The life cycle of the malaria parasite is complex, involving both *Anopheles* mosquitoes (the sporogonic cycle) and humans (the exoerythrocytic and erythrocytic cycles) [140]. During these cycles, parasites exist in various forms. Initially, a mosquito feeds on a human host and releases sporozoites into the bloodstream. The sporozoites travel to the liver initiating the exoerythrocytic cycle, where they invade hepatocytes. Multiplication results in schizonts and subsequently merozoites and cellular rupture. The merozoites infect erythrocytes initiating the erythrocytic cycle. During this stage, the parasites form characteristic trophozoites and schizonts leading to cellular rupture. Gametocytes may be formed. During a later feed, another *Anopheles* mosquito ingests the parasites (initiating the sporogenic cycle), which replicate in the mosquito's midgut, before migrating to the salivary glands in preparation for further transmission. Infections with *P. vivax* and *P. ovale* may reactivate following a dormant liver phase [141].

Pathogenesis

Rupture of hepatic cells can potentially lead to malarial hepatitis and hepatic encephalopathy. Erythrocytic rupture results in anemia and cerebral malaria. Adverse effects on pregnancy are directly related to the extent of placental infection and partly on the degree of maternal anemia [142, 143]. Placental malaria, characterized by parasitized red cells in placental blood in the intervillous space, is more commonly encountered than parasites in the maternal peripheral circulation. Consequences include increased risks of LBW and IUGR, anemia during infancy, and congenital malaria [144].

Secondary effects of maternal malaria include suppression of immune responses to vaccination, including tetanus toxoid, and can reduce placental transfer of specific antibodies to the fetus (e.g., for respiratory syncytial virus, measles, and pneumococcus) [145].

Transmission

Infected female mosquitoes vector malaria parasites from person to person and may be more attracted to pregnant versus nonpregnant women [146]. Transmission can also occur through transfusion of infected blood products or via infected needles.

Clinical Features

Pregnant women in endemic (stable or high transmission) areas are typically asymptomatic. However, they may develop anemia and become symptomatic. In severe disease, maternal morbidity and mortality increase. In epidemic (unstable or low transmission) areas, nonimmune pregnant women are at high risk of cerebral malaria, hypoglycemia, pulmonary edema, severe hemolytic anemia, and perinatal death [143]. Risk of stillbirth may be increased up to sevenfold in unstable areas [147]. Symptoms and signs (e.g., fever, chills, headache, sweats, vomiting) are nonspecific. The periodicity of malarial fever relates to the periodic rupture of parasitized red cells. Disease and death normally occur during the erythrocytic cycle as opposed to the exoerythrocytic cycle.

Maternal *P. falciparum* infection is an important contributing factor to LBW in first pregnancies and, to a lesser extent in second pregnancies, in Africa, resulting in IUGR, prematurity, increased neonatal and perinatal mortality, and infant anemia [144, 148–150]. Congenital malaria may occur in 7–10 % of neonates and be diagnosed by malarial parasites in cord blood. Fever, anemia, jaundice, hepatosplenomegaly, and early death occasionally occur [144].

Diagnosis

Diagnosis of malaria involves patient assessment in the context of appropriate laboratory testing. Malaria-specific testing traditionally involves the assessment of thick and thin smears of Giemsa-stained blood using a light microscope. The thick smear aids detection and enumeration of parasites, while the thin smear permits species determination.

Rapid diagnostic tests are increasingly used for the detection of malaria. These tests are typically immunochromatographic but may fail depending on degree of parasitemia or if certain species (e.g., *P. ovale* or *P. malaria*) are involved. Microscopy is usually required to confirm and quantify the species involved.

Other testing modalities include serology and nucleic acid testing. Serology identifies circulating antibody. While early infections can be missed when testing is performed prior to antibody formation, serological testing remains useful when screening blood products intended for transfusion. Nucleic acid tests have high sensitivity and specificity, although they are relatively expensive, less widely available,

and typically slower to perform compared with traditional methods such as blood smear.

Treatment

Prompt and appropriate treatment of pregnant women with malaria is critical. Treatments may include such agents as quinines, clindamycin, or an artemisinin. The WHO has prepared guidelines for the treatment of malaria in pregnancy, during lactation, and in young children [151].

The CDC updates treatment options, depending on location, for travelers (www.cdc.gov/travel).

Prevention

Nonimmune pregnant women should avoid malaria-endemic areas. In areas of moderate to high transmission, the WHO recommends a strategy for prevention and control in pregnant women involving intermittent preventive treatment with sulfadoxine-pyrimethamine, the use of insecticide-treated bed nets, and prompt and appropriate treatment [152].

Public Health Issues

The control of malaria is challenged by numerous factors including vector control, parasite drug resistance, resource limitations, and education. No effective vaccine is available although development continues [153]. Given recent gains toward malaria eradication, control strategies and research priorities must adapt to the changing epidemiology [154].

Parvovirus B19

Background

Parvovirus B19 was discovered by Australian virologist Yvonne Cossart in 1974 [155], although its association with human disease was not recognized until 1981. While the virus causes mild or asymptomatic childhood infections, it also causes more serious conditions including acute aplastic crisis (especially in the context of sickle cell disease), chronic anemia, hydrops fetalis, and intrauterine death.

Virology

Parvovirus B19 (family Parvoviridae, genus *Erythroparvovirus*) is a single-stranded linear DNA virus with very small genome (*parvum* is Latin meaning "small"). The virus is non-enveloped and has an icosahedral protein capsid resulting in heat resistance and detergent inactivation and contributing to its transmissibility [156].

Epidemiology and Transmission

Parvovirus B19 is a common virus, although transmissibility to adults is relatively low [157]. Infection, which is very common in childhood, may be sporadic or epidemic, often occurring in late winter and early spring in temperate climates. Children aged 5–15 years are most commonly infected and seroprevalence by adulthood is around 50–60 %. However, 30–50 % of pregnant women are nonimmune [158].

Transmission can occur via respiratory droplets, infected blood and blood products, bone marrow transplantation, tattooing and vertically during pregnancy [158].

Pathogenesis

Replication of B19 occurs in human erythroid progenitor cells in the human bone marrow and fetal liver [159]. Replication inhibits erythropoiesis. The virus has a tropism for the proerythroblast, which expresses the primary receptor globoside (i.e., P antigen) and co-receptors Ku80 autoantigen and α5β1 integrin [160]. Infection results in cytopathic changes and arrested cell line progression. Globoside is also present in cell lines not permissive for replication such as placental cells, endothelial cells, fetal myocardial cells, and megakaryocytes. It has been postulated that the placental globoside may be involved in vertical transmission of B19 from the mother to fetus [161]; the virus then targets fetal erythroid progenitor cells resulting in fetal anemia. Additionally, fetal myocardial globoside is likely responsible for fetal myocarditis resulting in cardiac failure [162].

Individuals who lack P antigen are rare and apparently cannot be infected with parvovirus B19 [163].

Clinical Features

Parvovirus B19 has an incubation period of 4–21 days. In otherwise healthy individuals, infection is often associated with a mild nonspecific prodromal illness corresponding with viremia [164] frequently characterized by fever, malaise, and myalgia. Concurrent destruction of erythroblasts occurs in the bone marrow resulting in a reticulocytopenia without anemia [164]. Later, rash and arthralgia may occur corresponding with the peak production of specific antibody and possibly a result of immune complex deposition.

Importantly, the clinical manifestations of parvovirus B19 vary widely, and infection is frequently subclinical. The most common clinical presentation in normal, healthy children is called *erythema infectiosum*, fifth disease or "slapped cheek" (because of the bright red cheeks the infection

causes). Parvovirus B19 can also cause an acute polyarthropathy, usually in adult females. The arthropathy is symmetrical and nondestructive and may last for weeks. Patients with increased erythropoiesis (e.g., due to sickle cell anemia) may experience a transient aplastic crisis. Infection in patients who cannot mount an antibody response (e.g., immunodeficient hosts) may result in chronic anemia [165].

One-third of maternal infections during pregnancy result in transmission to the fetus, with about 3 % resulting in fetal complications [166]. Fetal infection can cause anemia, nonimmune hydrops, and death.

Hydrops Fetalis

Hydrops fetalis may result from a combination of fetal anemia, a naturally shorter lifespan of fetal red cells, viral myocarditis, and impaired fetal hepatic function [162]. Nonimmune hydrops fetalis usually develops 2–4 weeks after maternal infection. Earlier infections (before 19–20 weeks' gestation) are associated with a higher loss rate than later infections [162]. On ultrasound, ascites, skin edema, pleural and pericardial effusions, and placental edema may be seen [167].

Fetal Death

Parvovirus B19 infection before 20 weeks' gestation is associated with spontaneous fetal loss in 14.8 % versus 2.3 % when infection occurs after 20 weeks' gestation [162]. Death usually occurs 4–6 weeks after infection and is not always associated with hydrops fetalis [163].

Death in the third trimester has been associated with parvovirus B19. In a prospective, hospital-based, cohort study, 7.5 % of all third-trimester intrauterine deaths had detectable parvovirus B19 DNA and were otherwise unexplained [168]. Notably, none of these fetuses was hydropic, and the authors suggest that investigation for parvovirus B19 infection should be included in the investigation of all intrauterine fetal deaths. Chronic congenital anemia secondary to parvovirus B19 infection has been reported [169].

Diagnosis

Several laboratory methods are available, including nucleic acid testing, and serology. Cell culture is not possible using standard culture media due to the virus' cellular tropisms. Cytological methods of diagnosis are available and include examination for intranuclear inclusions or assessment using electron microscopy [167].

Demonstration of specific anti-parvovirus B19 antibodies assists in diagnosis. The presence of anti-parvovirus B19 IgM is the best marker of recent or acute infection, and seroconversion from anti-parvovirus IgG negative to IgG positive in paired acute and convalescent sera is also indicative of recent infection [156]. Examination for IgM from fetal samples may result in failure to diagnose given fetal IgM does not appear until after 22 weeks' gestation [170].

Nucleic acid amplification testing is possible by PCR and is considered sensitive and specific. Diagnosis can be performed using amniotic fluid or fetal blood from cordocentesis [170]. The NAATs may be required for diagnosis of persistent infection where antibody production is absent or minimal [165].

Diagnosis of pregnant women may be supported clinically when the characteristic facial rash is present. For pregnant women with confirmed infection, ultrasound screening for evidence of fetal edema may be performed in the first 20 weeks of pregnancy at 1- to 2-week intervals for up to 8–12 weeks after infection [171].

Treatment

Supportive therapy is typically recommended for self-limited B19 and no specific antiviral therapy is available. Nonsteroidal anti-inflammatory medications (NSAIDs) may be indicated for arthropathy. Red cell transfusions may be appropriate in patients with transient aplastic crisis and intravenous immunoglobulin in patients with chronic red cell aplasia [172]. Specialist referral should be sought in cases of suspected hydrops fetalis and considerations might include intravascular transfusion [170].

Prevention

No vaccine is presently available. Frequent hand washing is recommended to reduce the spread of infection.

Public Health Issues

Balancing the risk-to-benefit ratio regarding public health interventions for B19 is complex given that adverse outcomes (when they occur) can be significant but are infrequent [157]. During outbreaks, persons at risk of infection should seek medical advice regarding public health measures. While it has been suggested that during outbreaks pregnant at-risk persons working with children (e.g., nursery teachers) might be at increased risk of infection [173], workplace avoidance will not necessarily prevent infection if they have contact with susceptible children in other settings (e.g., at home) [157].

Rubella

Background

Rubella or German measles, also known as third disease, is a typically benign, mild, self-limiting disease of childhood. However, fetal infection with rubella during early gestation can cause congenital rubella syndrome (CRS), which is

associated with profound morbidity and mortality. The Australian ophthalmologist Norman Gregg is first credited with associating congenital cataract and rubella infection in pregnancy [174].

Virology

Rubella (family Togaviridae, genus *Rubivirus*) is a spherical virus with single-stranded positive sense linear RNA, an icosahedral capsid, and a lipid envelope. Rubella virus is relatively unstable in the environment and is inactivated by disinfectants, solvents, extremes of pH and temperature, and ultraviolet light [175].

Epidemiology and Transmission

Rubella infection occurs worldwide and is endemic in many areas. Infection in temperate climates frequently occurs in late winter through early spring.

Rubella remains a threat to pregnant women and their fetuses [176]. Rubella vaccination is frequently provided in combination with measles vaccination. Since vaccination, the number of measles deaths has fallen from more than two million per annum to 139,300 per annum [176]. The number of infants worldwide born with CRS each year is more than 100,000 [177].

Humans are the only known reservoir. Transmission is via respiratory droplet from person to person.

Pathogenesis

After transmission, the virus replicates in the nasopharynx and regional lymph nodes, before spreading via the lymphatic system. Viremia occurs 5–7 days after infection. The incubation period is 12–23 days (average 14 days). Fetal infection occurs transplacentally during maternal viremia. Fetal infection can affect all organs; its impact is most severe in very early pregnancy, coincident with organogenesis. Rubella is teratogenic and causes fetal damage via two mechanisms: a generalized, progressive, necrotizing vasculitis, resulting in parenchymal hypoplasia, and cellular deletion through mitotic arrest and apoptosis [178, 179]. Infants infected with rubella in utero can shed the virus for up to 12 months or longer [180].

Clinical Features

Fetal Infection

A spectrum of outcomes can result from fetal rubella infection, including termination (both spontaneous and induced), still birth, or malformation. The risks are greatest during the first trimester, with 90 % of babies infected in the first 11 weeks' gestation developing CRS with the risk becoming negligible after 16 weeks [181]. The risk is also greater with primary infection versus reactivation [182].

Congenital rubella syndrome typically manifests in infancy. The WHO classifies cases for CRS surveillance purposes using clinical, epidemiological, and laboratory data [183] (Table 9.11 [177]).

Table 9.11 WHO syndrome groupings, laboratory criteria, and case classifications of CRS

Clinical features	A. Sensorineural hearing impairment, congenital heart disease, pigmentary retinopathy, cataract(s), congenital glaucoma
	B. Purpura, splenomegaly, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease, jaundice with onset within 24 h of birth
Laboratory criteria	1. Rubella IgM antibody detected
	2. Sustained rubella IgG antibody level as determined on at least two occasions between 6 and 12 months of age in the absence of receipt of rubella vaccine
	3. Rubella virus detection (e.g., nucleic acid detection by RT-PCR or rubella virus isolation) in an appropriate clinical sample (best results come from throat swabs, but nasal swabs, blood, urine, or cerebrospinal fluid specimens are also acceptable)
Case classifications	
Suspected	Any infant aged <1 year with ≥1 clinical features from group A and no other obvious cause
Laboratory confirmed	A suspected case that meets the laboratory criteria for CRS case confirmation
Clinically compatible	A suspected case that meets the clinical criteria for CRS and has not been adequately tested by laboratory
Epidemiologically linked	A suspected case that does not meet clinical criteria for CRS (i.e., has only one feature from group A) has not been adequately tested and has maternal history of laboratory-confirmed rubella during pregnancy
Discarded	A suspected case with negative results of adequate laboratory testing for evidence of rubella virus infection, or a suspected case that does not meet clinical criteria for CRS (i.e., has only one feature from group A), has not been adequately tested and does not have maternal history of laboratory-confirmed rubella during pregnancy

Adapted with permission from WHO [183], WHO Regional Office for Europe, 2012:36–37, (http://www.euro.who.int/en/health-topics/communicable-diseases/measles-and-rubella/publications/2012/surveillance-guidelines-for-measles,-rubella-and-congenital-rubella-syndrome-in-the-who-european-region,-update-december-2012) [177]

A global review of CRS sequelae from prospective studies with laboratory-confirmed infection found hearing impairment in 60 %, congenital heart disease in 45 %, microcephaly in 27 %, cataracts in 25 %, low birthweight (less than 2500 g) in 23 %, hepatosplenomegaly in 19 %, purpura in 17 %, mental retardation in 13 %, and meningoencephalitis in 10 % of infants with CRS [184]. Some developmental defects (e.g., hearing impairment) may not become apparent for months or years [182]. The most common delayed-onset disease in CRS is type 1 diabetes mellitus developing in adulthood. There is also a higher prevalence of type 2 diabetes, thyroid disorders, early menopause, and osteoporosis [185].

Postnatal Infection (Adults and Children)

Rubella is asymptomatic in up to 50 % of cases. When symptomatic, adults and children typically present with a rash first appearing on the face and associated with lymphadenopathy of the nasopharyngeal and upper respiratory tract nodes. The rash typically resolves in around 3 days. Complications of rubella infection include arthropathy (in up to 70 % women) and, rarely, thrombocytopenic purpura (more common in children), encephalitis, orchitis, and neuritis.

Diagnosis

Laboratory diagnosis of rubella is typically based on serology or nucleic acid detection. Serological confirmation relies upon detection of rubella-specific IgM or demonstration of a fourfold rise in rubella-specific IgG in paired acute and convalescent sera. Nucleic acid detection can be performed via reverse transcriptase PCR. While rubella can be cultured using Vero cells, the method is not widely performed given its costs, risks, and relative expense versus other techniques. However, if required, virus may be isolated from various clinical specimens including throat swabs, blood, nasopharyngeal fluid, urine, or CSF. Epidemiological workup can be performed using various methods including viral culture and nucleic acid analysis.

Expert advice should be sought from the nearest rubella reference laboratory regarding specimen collection, transport and handling, and testing protocols.

Treatment

Treatment is typically supportive. No specific antiviral agents are available. Nonsteroidal anti-inflammatory drugs may have benefit in cases of arthropathy. Expert advice is required for cases of CRS.

Prevention

Routine determination of immune status to rubella in all women of childbearing age and vaccination of the nonimmune and not pregnant is recommended. A theoretical risk to the fetus exists after vaccination in pregnancy; women should be counseled prior to vaccination to avoid pregnancy for 1 month [186]. Pregnant women should receive early antenatal screening for rubella immune status. The pregnant nonimmune should be advised to avoid persons with a rash illness and be vaccinated postpartum [187]. Infants with CRS can shed virus for >12 months, thus posing an infectious risk.

Public Health Issues

Widespread rubella vaccination over the past decade has largely eliminated rubella and CRS in many developed and some developing countries. Congenital rubella syndrome rates are highest in the WHO African and Southeast Asian regions where vaccine coverage is low. In 2012, the Measles & Rubella Initiative launched a Global Measles and Rubella Strategic Plan aimed to reduce measles deaths globally by at least 95 % compared with 2000 levels and eliminating regional measles and rubella/CRS [177].

Cytomegalovirus

Background

Childhood infection with cytomegalovirus (CMV) is common and frequently mild and self-limited. However, maternal CMV infection in pregnancy can cause congenital CMV with severe adverse outcomes including sensorineural hearing loss, neurological impairment, and death. Cytomegalovirus is tested for in a TORCH screen in newborns (i.e., toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus).

Virology

Cytomegalovirus (human herpes virus 5; family Herpesviridae, subfamily Betaherpesvirinae) is the largest human herpesvirus. It is a double-stranded DNA virus with an icosahedral capsid surrounded by a glycoprotein peplomer covered lipid envelope. As with other beta-herpesviruses, CMV is slower growing and establishes latency in leukocytes.

Epidemiology and Transmission

Global seroprevalence rates for CMV vary substantially. In women of reproductive age, seroprevalence is highest in areas of South America, Africa, and Asia (>90 %) and lowest in areas of North America and Western Europe (40–50 %) [188]. The lower seroprevalence in women of reproductive age in resource-wealthy countries may increase the risk of a primary infection during pregnancy. In the USA, 30–50 % of women of reproductive age have not been infected with CMV. Between 1 % and 4 % of this cohort experience primary CMV infection during pregnancy, with virus passing from the mother to fetus in one-third [189]. In the USA, such infection results in permanent disability in 1 in 750, resulting in more than 5000 affected children per year [190]. The prevalence of congenital CMV in industrialized countries is estimated to be between 0.6 % and 0.7 % [191]. Meanwhile, 80 % of neonates born with congenital CMV show no effects [189], although 10–15 % of these will develop symptoms (e.g., sensorineural hearing loss) later in life [192]. Between 1990 and 2006, 777 congenital CMV-associated deaths occurred in the USA [193].

Cytomegalovirus is transmitted through contact with infected body fluids (e.g., saliva, genital secretions, and urine). Peaks in transmission occur during infancy when children are exposed during childcare and in young adulthood coinciding with onset of sexual activity and kissing. Additionally, transmission can occur via infected blood products and through organ transplantation.

Vertical transmission of CMV is largely transplacental, with a greater risk (~1.83×) in primary infection versus non-primary infection [194]. Worse outcomes occur in children whose mothers experience a primary CMV infection during pregnancy and those where infection occurs in the first half of pregnancy [195]. Less commonly, perinatal transmission of CMV occurs after contact with infected maternal genital secretions or infected breast milk.

Pathogenesis

Several cell lines can be infected. Monocytes are the primary blood cell type infected, acting as reservoirs of latent virus and vehicles for viral dissemination [196]. Cytomegalovirus replication occurs in the host cell's nucleus and results in characteristic cytomegalic "owl's eye" cells, so-called because the nuclear inclusion is surrounded by a non-staining halo extending to the nuclear membrane. While cytomegalic cells are indicative of active infection, they are not always present.

In pregnancy, CMV is transmitted in infected leukocytes via the placenta to the fetus [197]. Additionally maternal IgG-CMV immune complexes may cross the placenta via transcytosis [198]. In the fetus, after CMV replicates in the renal tubule epithelium, it is excreted via urine into the amniotic fluid, re-ingested by the fetus, and the sequence repeats [195].

Fetal cellular injury in congenital CMV may result from a direct teratogenic effect or from impaired perfusion after vascular injury especially given the virus infects endothelium [198]. The CNS is the major target for cellular injury resulting in extensive neurodevelopmental sequelae.

Cytomegalovirus, like all human herpes viruses, can establish latency following primary infection principally in the salivary glands and renal tubules. Once infected, the host carries the virus for life and may intermittently shed virus in saliva, urine, semen, cervical secretions, or breast milk. Reactivation occurs in healthy and immunosuppressed individuals and may lead to vertical transmission in pregnancy.

Clinical Features

Outcomes associated with CMV infection vary widely. Various illnesses may occur in the immunocompromised, including fever and a septicemia-like presentation, pneumonitis, gastrointestinal disease including ulceration and hemorrhage, and CMV retinitis or CMV-induced immunosuppressive syndrome. In the otherwise well (including the pregnant), CMV can be clinically silent. Alternatively, it can cause a mild, nonspecific illness or more rarely syndromes similar to that seen in the immunocompromised. Infection in young adults may present with a syndrome similar to that seen with Epstein-Barr virus.

The early clinical findings in symptomatic congenital CMV may include IUGR and preterm delivery, petechiae, hyperbilirubinemia, hepatosplenomegaly, hepatitis, jaundice, microcephaly, chorioretinitis, ventriculomegaly, periventricular calcifications, and seizures. Late findings include developmental delay, mental retardation, seizures, and sensorineural hearing loss [195].

Diagnosis

Modalities available for the diagnosis of CMV infection include serology (specimen type: blood), cell culture (blood, saliva, urine), antigenemia (blood), PCR (blood, saliva, tissue, urine), immunohistochemistry (tissue), nucleic acid sequence-based amplification (blood, tissue), or hybrid capture assay (blood, tissue) [199]. The specific testing method selected depends on the patient population (e.g., immunosuppressed adult versus fetus). While various methods are available for testing in maternal and fetal cases, the

Table 9.12 Methods for CMV detection in maternal and fetal infections

	Method	Advantages and disadvantages
Maternal		
Serology	De novo appearance of IgG	Advantages: may indicate primary infection
		Disadvantages: may be negative if reinfected with a different strain
	Presence of IgM	Advantages: may indicate primary infection
		Disadvantages: may be present in non-primary infection; false-positive possible; cross-reactions with other viruses; IgM may persist for 9 months
	Low IgG avidity	Advantages: may indicate primary infection
		Disadvantages: timing-dependent variation in sensitivity regarding transmission to fetus
Nucleic acid testing	Detection by PCR	Advantages: indicates active maternal infection
		Disadvantages: <50 % pregnant women have CMV in blood at time of serological diagnosis; detection is timing dependent
Antigenemia testing	Detection of pp65	Similar to "Detection by PCR"
Fetal		
Isolation	Culture from amniotic fluid	Advantages: indicates fetal infection
		Disadvantages: poor sensitivity (70–80 %)
Nucleic acid testing	DNA detection in amniotic fluid	Advantages: indicates fetal infection; good sensitivity (90–100 %); permits quantification
		Disadvantages: timing-dependent false negatives possible
Fetal blood sampling	Blood	Advantages: permits assessment of viremia, antigenemia, DNAemia, and IgM
		Disadvantages: may result in fetal loss
Imaging	Ultrasound	Advantages: identifies structural or growth abnormalities
		Disadvantages: many infected fetuses have no abnormalities; symptomatic congenital infections may have no abnormalities
	MRI	Advantages: sensitive detection of abnormalities
		Disadvantages: see disadvantages for "Ultrasound"

See Ross et al. [199]

advantages and disadvantages of each must be carefully assessed (Table 9.12 [199]). Neonatal testing includes: PCR or culture of urine, blood, or saliva; assessment of neonatal serum for IgM; cerebral ultrasound; and physical, neurological, and anthropometric monitoring [200].

Treatment

Historically there have been few specific treatment approaches for CMV in pregnancy aside from counseling followed by either termination or a "wait and see" approach [201]. Assessments of specific agents including oral valacyclovir, intravenous ganciclovir, and CMV immunoglobulin G are limited. Ganciclovir may prevent hearing deterioration in symptomatic neonates with CNS disease [202].

Prevention

No vaccine is currently licensed for use against CMV.

The CDC recommends that pregnant women minimize contact with potentially infected child excretions and secretions and wash their hands with soap and water for 15–20 s after changing diapers, feeding a young child, wiping a young child's nose or drool, or handling children's toys [203]. Additional recommendations include [204]:

- Women who develop a mononucleosis-like illness during pregnancy should be evaluated for primary CMV infection.
- Recovery of CMV from the cervix or urine of women at or before the time of delivery does not warrant a cesarean section.
- In most cases, the demonstrated benefits of breast-feeding by CMV-positive mothers outweigh the minimal risk of acquiring CMV from the breast milk. Physicians and mothers should take into account the potential risk of transmitting CMV when making decisions about breast-feeding very premature infants.

Public Health Issues

Women co-infected with HIV and CMV are more likely to suffer CMV recurrences, increasing the likelihood of congenital CMV in pregnancy [205]. Pregnant women and women of child bearing age working in areas of potential exposure to CMV infected persons should practise strict infection control methods.

Varicella-Zoster Virus

Background

Varicella-zoster virus (VZV) is the third of the human herpes viruses. Infection with VZV causes varicella (chickenpox). Like all human herpes viruses, VZV remains latent after infection with reactivation causing herpes zoster (shingles). Primary VZV infection in pregnancy can have severe consequences for both the mother and baby. Nosocomial transmission of varicella is well recognized.

Virology

Varicella-zoster virus (family Herpesviridae, subfamily Alphaherpesvirinae, genus *Varicellovirus*) is a linear double-stranded DNA virus with a spherical virion and enveloped with an icosahedral capsid. Its envelope is studded with glycoproteins. The Alphaherpesvirinae (which also include HSV-1 and HSV-2) grow rapidly, cause lysis of infected cells, and establish latent infection in the ganglia of sensory nerves. Reactivation triggers replication and shedding of infectious virus (herpes zoster).

Epidemiology and Transmission

Varicella-zoster virus is a highly contagious infection that is transmitted person to person by contact, aerosol, or droplet from vesicular fluid of skin lesions or by infected respiratory tract secretions. Hematogenous spread in pregnancy can occur causing congenital varicella syndrome although this is relatively rare. Varicella vaccination in the USA has reduced varicella infections to similar levels seen in infants ineligible for vaccination [206]. Reductions in infection rates are partly attributable to herd immunity. Chickenpox is infectious from one to two days before rash onset until all blisters have crusted (typically 5-6 days after rash onset)

Pathogenesis

Incubation is 14–16 days (range 10–21 days). The virus is lymphotropic and neurotropic. The mechanisms of pathogenesis, although still not fully understood, were recently reviewed [207]. After primary exposure, virus replicates in the respiratory and oropharyngeal mucosa. It then infects lymphoidal tissue and disseminates via the lymphatics and then bloodstream, replicating in mononuclear leukocytes and capillary endothelial cells. The virus also spreads to the liver. Infected T-lymphocytes probably transport the virus to the skin where it is initially controlled, but then overcome, resulting in rash. Additionally, virus infects sensory nerve root ganglia through retrograde spread.

After primary infection, the virus remains dormant in the cerebral or posterior root ganglia. The virus can reactivate resulting in a dermatomal rash. Reactivation most commonly occurs decades after primary infection or in the immunocompromised but can also occur in children.

Congenital disease is secondary to maternal viremia whereby VZV crosses the placenta. Outcomes vary with gestational age, ranging from unaffected to death. While teratogenesis is highest in early pregnancy coinciding with organogenesis, fetal death can also occur when infection occurs in the days prior to delivery in the nonimmune mother. After birth, the newborn (who is not protected by maternal antibody) suffers viremia.

Clinical Features

The clinical features of varicella vary with form of infection. For example, primary infection in childhood (chickenpox) is typically a self-limiting illness with a rash. Adolescents, adults, and the immunocompromised are more likely to have poor outcomes, with complications including secondary bacterial infection of rash lesions, pneumonitis, hepatitis, meningoencephalitis, cerebellar ataxia, and Reye's syndrome. Reactivation (shingles) typically produces a rash that is limited to particular dermatome and is associated with sensory changes, pain, and possibly headache and fevers. Postherpetic neuralgia can ensue.

Four forms can affect pregnancy or the newborn: varicella pneumonitis, congenital pneumonitis, neonatal varicella, and infant herpes zoster.

Varicella Pneumonitis

Maternal infection during pregnancy is associated with an increased risk of pneumonitis. Clinically, respiratory symptoms develop about 4–5 days after the onset of the varicella rash and include tachypnea, dyspnea, cough, and fever [208]. Radiologically there are bilateral, diffuse, peribronchial nodular infiltrates [195]. Radiological and clinical findings may be disparate, with abnormal radiology in the absence of abnormal clinical findings [195, 208]. Varicella pneumonitis can be life threatening when it occurs in the second or third trimester of pregnancy [208].

Congenital Varicella

Congenital varicella can affect the skin, limbs, eyes, and central and autonomic nervous systems (Table 9.13 [209]).

A large prospective study of 1373 women whose pregnancies were complicated by varicella before week 36 found that all cases of congenital varicella occurred before week 20 and the overall risk was approximately 1 % [209,

Table 9.13 Stigmata of congenital varicella

System	Characteristic
Skin	Cicatricial lesions that may be depressed, pigmented, or hypopigmented and follow a dermatomal distribution
Limb	Hypoplasia of bones or muscles, absent or malformed digits
Eyes	Cataracts, chorioretinitis, Horner's syndrome, microphthalmia, nystagmus, ptosis
CNS	Cortical atrophy, mental retardation, microcephaly, seizures
ANS	Esophageal dilation and reflux, hydroureter, neurogenic bladder

See Smith and Arvin [209]; *CNS* central nervous system, *ANS* autonomic nervous system

210]. The highest risk (2 %) was observed between weeks 13 and 20.

Neonatal Varicella

Maternal varicella rash developing from 5 days before delivery to 2 days after delivery has an attack rate in the newborn of approximately 20 % with a mortality rate of about 30 % [211]. Overwhelming neonatal infection ensues as there is insufficient time for maternal VZV IgG to develop and cross the placenta [186]. Clinical features may include a typical varicella rash, respiratory distress and pneumonia, hepatitis, and widespread focal necrosis [212].

Infant Herpes Zoster

Infants born to mothers who suffered VZV infection between weeks 14 and 33 can demonstrate infant zoster in the first 2 years of life (see [209]). Disease is typically benign, presenting with a vesicular rash in a dermatomal distribution (see [213]). Infants may be irritable and febrile and demonstrate lymphadenopathy.

Diagnosis

Diagnosis of VZV can be made by viral isolation, fluorescent staining, nucleic acid testing, or serology. Virus can be isolated using tissue culture, although the method is slower than nucleic acid testing and lacks sensitivity. Direct fluorescent antibody staining is a more rapid technique that can be performed directly on cells scraped from skin lesions. While specific, the method is less sensitive than nucleic acid methods. PCR can be performed on multiple samples types including fluid from cutaneous lesions, CSF, blood or tissue. Serological evidence can also be used for diagnosis. IgM may signify recent infection but can also be present in reactivation. A single IgG assay provides evidence of infection but cannot immediately delineate between recent and past infections. Consequently, evidence of a fourfold rise in paired acute versus convalescent sera, or low IgG avidity, may be required to demonstrate recent infection.

Treatment

Recommendations for treating VZV vary with patient population, patient characteristics, and location. Populations include otherwise healthy adults, immunocompromised patients, patients exhibiting varicella complications, pregnant women, and affected neonates. In pregnancy, oral acyclovir has been recommended for women with significant infection (e.g., pneumonitis) and intravenous acyclovir recommended in those with severe complications [214]. Other guidelines recommend a 7-day course of oral acyclovir (or possibly valacyclovir or famciclovir) if commenced within 72 h of rash onset [215].

Prevention

Live attenuated varicella vaccines were introduced in the USA in 1995. Varicella vaccine is contraindicated in pregnancy. Postexposure prophylaxis with VZIG is recommended within 96 h of exposure for nonimmune pregnant women and for those whose VZV immune status cannot be determined within that time frame [214]. The risk of maternal infection is reduced, with possible flow-on effects to the fetus [see 214]. VZIG administration to neonates is recommended when the onset of maternal disease is between 5 days before and 2 days after delivery [214].

Public Health Issues

Infection control measures recommended for neonates born to mothers with varicella include airborne and contact precautions in addition to standard precautions. These should be maintained until either 21 days of age or 28 days of age if they received VZIG. For exposed nonimmune patients, the precautions above are recommended for 8–21 days after onset of rash in the index patient and for 28 days in those who received VZIG [216].

Human Herpes Simplex Viruses 1 and 2

Background

Human herpes simplex virus 1 and 2 infections most commonly cause ulceration and blistering in the skin and mucus membranes known as cold sores (most commonly HSV-1) and in the genitals known as genital herpes (most commonly HSV-2).

Virology

The human herpes simplex virus (family Herpesviridae, subfamily Alphaherpesvirinae, genus *Simplexvirus*) is an enveloped and spherically shaped linear double-stranded DNA virus with an icosahedral capsid. The envelope contains many different glycoproteins. Typical of alpha-herpesviruses, it grows rapidly, causes lysis of infected cells, and establishes latent infection in the ganglia of sensory nerves. The virus can periodically reactivate, with replication and viral shedding.

Epidemiology and Transmission

Estimates of the incidence of neonatal HSV infection vary considerably from 9.6 per 100,000 births in the USA [217] to 33 per 100,000 births in the UK [218]. Variation exists by region and race and medical insurance status [217].

Historically, genital herpes was associated with HSV-2. Herpes simplex virus 2 occurs more commonly in woman than men, in non-Hispanic blacks than whites, and in persons with multiple sex partners [219]. In the US, the prevalence of HSV-2 decreased from 1988 to 2004 but has subsequently stabilized [219]. Between 2005 and 2010, the seroprevalence of HSV-2 in the USA was 15.7 % [220]. Prevalence rates vary considerably worldwide, with relatively low rates in Europe (males 13 %, females 18 %) versus sub-Saharan Africa (males 55 %, females 70 %). Globally, 536 million individuals aged 15–49 years are infected with HSV-2 [221].

Worldwide, HSV-1 is causing an increasing proportion of genital herpes cases [222]. In the USA, HSV-1 causes 20–80 % of genital herpes cases dependent on location [223]. Orolabial HSV-1 occurs commonly in early childhood, with reactivation causing cold sores that release virus. Orogenital sex or autoinfection may result in HSV-1 genital infection.

Maternal HSV infection in pregnancy can be transmitted to the neonate at delivery via contact with infectious ulcers or through asymptomatic shedding [224]. Postnatal infection can be acquired via viral transmission from active infective lesions on parents or caregivers [224].

Genital Herpes

Genital herpes is transmitted sexually when virus-infected secretions come into contact with susceptible mucosal surfaces or breached epithelium. The risk of infection is affected by age, race, number of lifetime sex partners, frequency of sexual intercourse, and income [225].

After infection, HSV may be intermittently shed from the genital tract of both men and women in the absence of prodrome, symptoms, or lesions. In pregnancy, rates of HSV shedding at delivery have been reported at between 0.3 % and 0.5 % [226, 227] with higher rates of 1.4 % reported in women with a history of recurrent HSV infection [228].

Herpes simplex virus infections are defined serologically as primary, non-primary, and recurrent. Serological primary infection with HSV-1 or HSV-2 occurs in someone who is seronegative to both. Non-primary infection is defined as confirmed infection with HSV-1 or HSV-2 occurring in the presence of heterologous antibody (e.g., infection with HSV-2 in a HSV-2 seronegative person who has antibody to HSV-1). Non-primary infection is generally clinically milder [229].

Primary HSV infection in pregnancy confers the highest risk of neonatal infection. The chance of vertical transmission is greatest when maternal infection with HSV-1 or HSV-2 occurs close to the time of labor, with a risk of 50 % in primary infection and approximately 30 % in non-primary first episodes [229, 230]. Genital herpes infection acquired in the first half of pregnancy, or reactivation of genital HSV acquired prior to pregnancy, is associated with a considerably lower risk (1–5 %) of vertical transmission [229].

Neonatal Herpes

Risk factors for mother to neonate transmission include the type of maternal infection (e.g., primary versus recurrent), maternal antibody status, duration of ROM, the integrity of mucocutaneous barriers, and whether the delivery mode is vaginal or cesarean [231]. Greater than 85 % of neonatal herpes infections occur after perinatal exposure of the baby to HSV-infected maternal genital secretions [230]. This results from asymptomatic HSV shedding near the time of delivery in approximately 70 % of cases [232].

Approximately 10 % of neonatal herpes is acquired postnatally after close contact with family or hospital staff suffering orolabial or cutaneous HSV infection (most commonly HSV-1) [230, 233]. Approximately 5 % of cases of neonatal herpes are caused by intrauterine infection, which is characterized by cutaneous, ocular, and neurological findings, and may be associated with hydrops fetalis [230]. Transplacental infection of herpes virus is extremely rare after recurrent disease [229].

Pathogenesis

After transmission, HSV replicates locally in epidermal cells of the skin or mucous membranes. The virus then transits via retrograde axonal flow up the peripheral sensory nerve fibers to the corresponding sensory ganglia in the brainstem or spinal cord whereupon the viral genome persists indefinitely. Reactivation of infection can occur at any time; triggers include stress, ultraviolet light, fever, nerve

injury, or immunosuppression. Following reactivation, replication occurs in the latently infected neurons, and virus is transported down the axon to the periphery where it multiplies in epithelial cells in the same vicinity as those infected originally [231, 234].

During infection, the viral surface glycoproteins facilitate penetration into cells while also eliciting immune responses [231]. While antigenic cross-reactivity exists between many HSV-1 and HSV-2 glycoproteins, glycoprotein gG provides antigenic specificity [235].

Clinical Features

Neonatal herpes is classified into three subgroups, which have diagnostic, therapeutic, and prognostic implications [229, 230]:

- Disseminated disease with or without CNS involvement (25 % of perinatal infections; the highest mortality and morbidity)
- Disease localized to the central nervous system (CNS) (30 % of perinatal infections; lower mortality but significant morbidity)
- Disease localized to the skin, eye, or mouth (SEM) (45 % of perinatal infections; lower morbidity and mortality when specific antiviral therapy is used)

Neonates develop symptoms within the first month of life with a large proportion becoming symptomatic within the first 2 weeks [229, 230]. No single constellation of clinical features identifies all cases of neonatal herpes [236]. Skin vesicles and seizures in babies with CNS disease are among the most suggestive findings of neonatal HSV infection. Other common signs and symptoms are lethargy, fever, conjunctivitis, disseminated intravascular coagulation, and pneumonia. Importantly, skin vesicles are absent in 17 % of babies with SEM disease, 32 % of babies with CNS disease, and 39 % of babies with disseminated HSV disease [236]. Ocular involvement can affect the anterior or posterior orbit, can be unilateral or bilateral, and can progress over several weeks and cause cortical blindness [237].

Diagnosis

Diagnosis of HSV is via nucleic acid testing (NAT), viral antigen staining, serology, and viral isolation. Various sample types can be analyzed including samples from skin vesicles, nose, throat, conjunctiva, blood, or CSF. PCR-based nucleic acid tests have high sensitivity and specificity and can be performed on CSF. However, testing may be negative in early infection or when viral loads fall below the assay's limit of detection. Additionally, positive results from blood do not aid disease classification [238]. Historically, viral culture represented the gold standard. However, the method is slower than NAT, arguably more prone to contamination, requires maintenance of cell lines, and may have lower sensitivity despite excellent specificity [see 239]. The use of direct fluorescent antigen testing permits rapid assessment of smears while negating the inconvenience of cell line maintenance, although the method is reliant on good-quality specimen [239]. Serological assessment of HSV-1 and HSV-2 antibodies during acute versus convalescent phases permits categorization of infection (e.g., primary, non-primary, and recurrent) and may be useful in identifying asymptomatic carriers and in seroprevalence studies.

Treatment

Consider testing urine and stools and rectal, oral, and nasopharyngeal swabs. Treatment of asymptomatic term infants born to mothers with suspected first-episode genital HSV may involve intravenous acyclovir if delivery is vaginal or membranes rupture pre-cesarean delivery [240]. In cases where asymptomatic term infants are born to mothers with recurrent HSV, it has been recommended that CSF and blood be assessed for virus if HSV is detected in mucous membrane swabs at 24 h; again the neonate is treated with acyclovir [240]. When neonates have symptoms compatible with HSV, early treatment with IV acyclovir has been recommended with prolongation of treatment in CNS involvement [240]. Topical ophthalmic anti-herpesvirus antivirals such as trifluridine are indicated where ocular involvement is suspected [240].

Prevention

Interventions to prevent neonatal herpes differ according to the stage of pregnancy and the presence of other risk factors (see overview in [241]). Antenatally, HSV seropositive partners of seronegative women should utilize condoms and suppressive antivirals. Additionally, they should abstain from intercourse when their partner is symptomatic or during the third trimester. Women with recurrent genital HSV should use suppressive antivirals from at least week 36, with subsequent neonatal follow-up. A cesarean might be indicted in primary HSV during pregnancy or in failure to seroconvert post-primary infection. Vaginal delivery may be appropriate when seroconversion occurs well prior to delivery, although scalp electrodes and forceps and vacuum delivery are not recommended. When vaginal delivery occurs with active lesions, the neonate should be treated with IV acyclovir. Postnatally persons with orofacial herpes lesions or herpetic

whitlow should maintain good hygiene and avoid contacting the lesions with the neonate. No vaccine is licensed for clinical use.

Public Health Issues

Despite the relatively low incidence of neonatal herpes, outcomes can be poor. Neonatal herpes prevalence remains higher in resource-poor areas indicating its association with poverty. HSV-2 has been implicated in facilitating HIV infection [242]. Public health interventions targeting HSV-2 transmission may therefore reduce rates of infection, neonatal herpes, and concomitant disease burdens such as HIV.

Human Immunodeficiency Virus

Human immunodeficiency virus has been implicated in perinatal transmission. Two types are described: HIV Type 1 (HIV-1) and HIV Type 2 (HIV-2).

Virology

Human immunodeficiency virus (family Retroviridae, genus *Lentivirus*) was first observed clinically in the early 1980s. Both HIV-1 and HIV-2 probably evolved from simian immunodeficiency viruses of chimpanzees, although HIV-1 probably emerged in Cameroon and subsequently spread worldwide, while HIV-2 emerged in Guinea-Bissau and Senegal and has remained relatively restricted [243]. Four subtypes of HIV-1 are described (M, N, O, and P), and each may have originated from a unique cross-species transmission event. Retrovirus virions have a diploid, linear, single-stranded RNA genome with three major structural genes (*gag*, *env*, and *pol*) and several accessory genes. The genome-nucleoprotein complex is closely associated with molecules of the viral enzymes: reverse transcriptase, integrase, and protease. The virus is enveloped with glycoprotein peplomers.

Transmission

Transmission can occur through numerous mechanisms, typically requiring person-to-person transmission of infected material. Transmission can be horizontal or vertical (Table 9.14).

Vertical transmission accounts for approximately 90 % of HIV-1 infections in children and neonatal infection and may occur in up to 30 % of infected women; transmission falls to around 1 % if antiretroviral agents are introduced. Multiple viral, immune, and clinical factors in both the mother and baby influence vertical transmission. The strongest predictors of risk are maternal plasma viral load, obstetric factors, and breastfeeding [244]. Although the incidence of vertical transmission has been reduced in the developed world, it remains high in developing countries. The vertical transmissibility of HIV-2 is considerably lower than that of HIV-1, possibly due to lower circulating RNA levels [245].

Table 9.14 Mechanisms of transmission of HIV

Transmission	Description
Horizontal	Intimate contact via infected genital secretions or infected blood contacting the rectal, oral, or vaginal mucosa
	Iatrogenically via direct contact with infected blood, transfusion of infected blood or blood products, or contaminated equipment
	Needle sharing
Vertical	Transplacentally
	Perinatally during labor and delivery
	Postnatally via breastfeeding

Pathogenesis

At a cellular level, the pathogenesis of HIV is complex and involves numerous cellular processes (see [246] for a detailed description). After transmission, in HIV-1 the virions bind to CD4+ cells via glycoprotein 120 (gp120; coded by the *env* gene). Gp120 then binds to a co-receptor such as CXCR4 or CCR5. The virus then fuses with the cell membrane and uncoats. In the cytosol, complementary DNA is synthesized via reverse transcriptase (encoded by p51 and p66), which is transported to the nucleus where it integrates into the host DNA via integrase. Proviral transcription occurs, and the resulting mRNAs are exported from the nucleus, followed by translation and reassembly. Finally, the virus buds from the cell, whereupon it can infect another CD4+ cell. Disease progression over time is complex (see [247]), but typically results in depletion of CD4+ cells immunocompromising the host. Some mechanisms employed by HIV-2 vary from HIV-1 [248].

Clinical Features

HIV-1

Rapid disease progression is seen in neonates, with clinical manifestations as early as 4–6 weeks. Clinical manifestations include failure to thrive, generalized lymphadenopathy, hepatomegaly, splenomegaly, parotitis, oral candidiasis, recurrent diarrhea, cardiomyopathy, hepatitis, CNS disease (including developmental delay), recurrent bacterial infections, opportunistic infections, and malignancy [249].

Opportunistic infections frequently occur, including *Pneumocystis jirovecii* (causing *Pneumocystis* pneumonia), CMV infection, chronic or disseminated HSV or VZV infection, and candidal esophagitis. Less commonly mycobacterium infections, chronic enteritis, and rarely disseminated CNS *Toxoplasmosis gondii* or cryptococcal infections occur [249].

The development of opportunistic infections, wasting, progressive neurological disease, high viral load, a low CD4+ T-cell count, and the onset of symptoms in the first year of life are associated with a poor prognosis [249].

HIV-2

Progression of HIV-2 is typically slower than HIV-1, although a similar spectrum of manifestations is present [245].

Diagnosis

Diagnostic strategies for HIV-1 and HIV-2 are typically regionally specific and vary by population. Algorithms typically employ a variety of methodologies, including serology (including assays for antigen and/or antibody detection) and nucleic acid detection (including RNA detection or proviral DNA detection). Highly sensitive screening assays are typically followed by more specific confirmatory assays. Historically, viral culture was utilized. In infants, maternal antibody can persist for up to 18 months. Consequently, antibody testing is not considered diagnostic, and nucleic acid testing is often recommended.

Local guidelines regarding HIV diagnosis should be consulted regarding recommendations involving antenatal counseling and perinatal testing to help minimize the risk of vertical transmission (e.g., [250–252]). Additionally, prompt expert advice should be obtained regarding early testing of neonates born to HIV-infected mothers especially given the rapid progression of disease in neonates.

Treatment

Antiretroviral agents represent the mainstay of chemotherapy. Such agents typically interfere with the cellular interactions required for viral replication. As such, they are frequently classified by the method of action (e.g., entry inhibitors, fusion inhibitors, reverse transcriptase inhibitors, integrase inhibitors, and protease inhibitors). Numerous guidelines exist (e.g., [253, 254]).

Prevention

The reduction of perinatal HIV transmission represents a major public health challenge. Primary HIV prevention strategies for women comprise a critical component. Appropriate prenatal care is required, with many guidelines recommending HIV screening early in pregnancy [21, 250]. Antiretroviral therapy substantially reduces the risk of mother-to-child transmission [255]. An elective cesarian may be indicated.

The WHO Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection include recommendations regarding breastfeeding in pregnancy [256].

Public Health Strategies

HIV infection (particularly HIV-1) remains a public health crisis across the developing and developed world. The issue has been complicated by education deficits, policy direction, and resource limitations including access to reliable testing and antiretroviral availability. Vertical transmission, particularly in the developing world, must be reduced. No vaccine is available. Blood products and organ donations are typically screened for HIV.

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