CHAPTER 19

Infection in pregnancy

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1 Introduction

In the past, bacterial infection during pregnancy was a major cause of both maternal and perinatal death. These deaths are now rare in most parts of the developed world, although maternal infection and colonization with pathogenic organisms continue to cause problems for both mothers and babies. Various infections are more prevalent among socio-economically disadvantaged pregnant women, and this may in part explain the greater frequency of adverse outcomes of pregnancy among these women.

Other organisms, such as fungi, viruses, and protozoa, may lead to serious disease during pregnancy and the perinatal period. In the last decade, infections with the human immunodeficiency virus (HIV) have become epidemic in many countries, particularly in the developing world. In many developing countries, HIV is now a major cause of maternal and infant mortality. Other organisms such as Chlamydia trachomatis and the genital mycoplasmas, have also been linked with disease in pregnancy and childbirth. Finally, pregnant women are subject to the same range of acute and chronic infections as non-pregnant women.


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2 HIV infection

Asymptomatic HIV infection and acquired immunodeficiency syndrome (AIDS) are now major health problems. AIDS is characterized by defects in the immune system with attendant susceptibility to infections by opportunistic micro-organisms and specific tumours. Asymptomatic HIV infection is important because of the risk of transmission from the mother to the fetus or neonate. Despite improvements in survival associated with the introduction of combinations of more potent antiretroviral therapies, for many HIV-infected individuals, complications still occur.

Pediatric-acquired immunodeficiency syndrome was first recognized in 1982 and numerous case series have been reported since. HIV infection is usually not recognized at birth, but can present months to years later with recurrent bacterial infections and sepsis, persistent or recurrent thrush, and failure to thrive.

The organism in adults is usually transmitted sexually, and is frequently associated with the presence of other sexually transmitted disease. It is also transmitted through infected blood and blood products, or the sharing of infected needles among drug users. Intrauterine transmission from mother to infant may occur during pregnancy, at birth (when most transmission occurs), or through breast milk. While the advantages of breastfeeding may outweigh the risk of transmission through breast milk, communities in less-developed countries need to identify ways to reduce the not insignificant incidence of postnatal transmission through breastfeeding.

There is now good evidence of reduced transmission of HIV infection from mother to baby by prenatal zidovudine treatment. Unfortunately, the cost of this drug is prohibitive in countries with the greatest burden of need. There may be a further reduction in vertical transmission when pregnant women are treated with the now standard, more potent antiretroviral combinations. There is also emerging evidence of reduced transmission through delivery by cesarean section.

Both symptomatic and asymptomatic women may transmit the infection to their infants. Offering screening only to women who are considered to be at high risk will only detect a small proportion of infected women. Universal screening for HIV in pregnancy is being widely advocated.

Globally, the major issue is the high prevalence of HIV infection in the poorest countries, where facilities for prevention and treatment are
least available. HIV infection has become a massive problem in developing countries. In some it is the single most important cause of maternal death.

3 Syphilis

The incidence of syphilis has declined dramatically in the developed world following the widespread introduction of penicillin in the 1950s. More recently, the incidence has increased again, largely in association with HIV infection. In the developing world, syphilis remains a major public health problem.

Syphilis during pregnancy is particularly important because transmission of Treponema pallidum from mother to baby may result in congenital syphilis, with its tragic sequelae. Such transmission may cause abortion, preterm birth, or perinatal death (20%). Subclinical congenital infection with resulting handicap is not uncommon. Congenital syphilis can be largely prevented by identification and treatment of the infected mother during pregnancy. Transmission to the fetus occurs particularly during the second trimester, although it may occur during the first trimester as well.

Most infected women are free of symptoms, and can only be identified by blood testing. A program of screening and treating those women found to be seropositive is cost-effective, even in places where syphilis in pregnancy is rare, because effective treatment is simple and readily available, while the consequences of untreated infection are so serious.

Treatment of mothers should consist of efficacious antibiotics, preferably a penicillin. Infants and women’s sexual partners should be followed up, and treated if found to be infected.

The clinical diagnosis of congenital syphilis is difficult because the presentation is variable, and many babies are free of symptoms. Treatment of infants is recommended when the adequacy of treatment of the mother is unknown or if the mother received treatment for the first time during the pregnancy with a drug other than penicillin.

4 Gonorrhoea

In some parts of the world, routine screening for gonorrhoea during pregnancy is deemed worthwhile because of the severe effects of
infection on both the mother and her baby. This can be accomplished by obtaining cervical swabs for culture at the first antenatal visit. In women considered to be at particular risk, either on demographic grounds or because of a history of sexually transmitted disease, repeat cultures can be taken.

Culture remains the 'gold standard' for diagnosis of gonorrhoea. The Gram stain is not sensitive enough for specimens obtained from the female genital tract. Although the infection may be asymptomatic, pregnancy appears to increase the likelihood of both arthritis and systemic disease. Where the prevalence of penicillin-resistant gonorrhoea is high, certain third-generation cephalosporins are recommended for treatment.

The most common gonococcal infection in neonates is conjunctivitis. Gonococcal ophthalmia characteristically manifests itself early, 2–5 days after birth. If left untreated, this infection may lead to permanent corneal damage and even perforation of the eye. The ideal method of preventing neonatal ophthalmia is detection and early treatment of maternal disease.

There is no evidence that routine prophylactic medication is better than careful observation and prompt treatment of ophthalmia in the newborn in most populations. Prophylaxis is required when mandated by law (as is the case in some countries or states) or in populations with a high prevalence of gonorrhoea. When such prophylaxis is necessary, antibiotic regimens that are active against both gonorrhoea and chlamydia should be used. Cohort studies of tetracycline, erythromycin, and penicillin suggest that these agents are both less irritating and more effective prophylactic agents than silver nitrate, and they are also effective against chlamydial infection.

5 Chlamydia trachomatis

Maternal infection with Chlamydia trachomatis is important primarily because of the potential adverse effects of infection on the newborn infant. The condition is often asymptomatic in the mother, and may not be detected clinically, although some infected women may have a mucopurulent cervicitis, salpingitis, or a urethral syndrome.

The prevalence of Chlamydia trachomatis in pregnant women varies widely; estimates ranging from 2% to nearly 40% have been reported. In the United States, high rates are found in young women, unmarried women, and black women, as well as in women from
lower socio-economic groups and those attending inner-city ante-
natal clinics.

The newborn infant can acquire chlamydial infection through
contact with infected maternal genital secretions at birth. Inclusion
conjunctivitis will develop in 18–50% of infants born to infected
mothers, making *Chlamydia trachomatis* the most common cause
of neonatal conjunctivitis. The estimated risk that an infant born to
an infected mother will develop chlamydial pneumonia ranges from
3 to 18%.

The diagnosis of maternal *Chlamydia trachomatis* infection is best
made by using one of the new amplified nucleic acid tests. Tissue
culture and antigen detection kits are less sensitive than the amplified
methods and, where available, an amplification method should be used
to test cervical specimens from pregnant women. There are no data
using the newer diagnostic tests to estimate the cost-effectiveness of
screening for chlamydia at different prevalence rates.

Randomized, controlled trials of antibiotic treatment suggest that
amoxicillin is as effective as erythromycin in eradicating colonization
by *Chlamydia trachomatis* during pregnancy; a single dose of
azithromycin is an alternative. Tetracycline is contra-indicated in preg-
nancy because of its hepatotoxicity and its effect on the development
of bone and teeth in the fetus.

The natural history of *Chlamydia trachomatis* infections in preg-
nancy is inadequately known and the role of the organism in the
adverse outcomes of pregnancy remains to be resolved. Well-designed
trials are still required to clarify the usefulness of screening for and
treating this condition.

6 Bacterial vaginosis

Bacterial vaginosis is a vaginal infection typified by large numbers of
organisms, such as *Gardnerella vaginalis, Mycoplasma hominis*, and
various anaerobes, and by decreased numbers of the normal popula-
tion of lactobacilli. Bacterial vaginosis is not thought to be sexually
transmitted, but may be associated with sexual activity. It has been
postulated as a cause of adverse pregnancy outcome, notably due to
preterm birth. However, bacterial vaginosis may be present in up
to 20% of pregnant women and, before screening and treatment are
advocated, it is important to determine whether the infection is, in fact,
pathogenic.
The suggestion that bacterial vaginosis might be a cause of pregnancy wastage is largely based on case-control studies in which a higher rate of colonization was found among women with adverse pregnancy outcomes than among those without abnormal outcomes. As is true of all such studies, other factors, both known and unknown, may have caused the adverse outcomes, irrespective of the presence or absence of bacterial vaginosis. For example, if such infections are simply markers for sexually transmitted disease in general, other organisms might be the actual causes.

Trials have shown that bacterial vaginosis may be treated effectively by antibiotics. However, this did not result in any improvement in pregnancy outcome, except in women with a past history of preterm birth, who were less likely to deliver preterm after treatment. It may, therefore, be worthwhile screening such women in subsequent pregnancies (see Chapter 13).

7 Herpes simplex

Herpes simplex infection of the newborn, acquired from the mother, is a rare but potentially serious condition, occurring in between 1 in 2500 and 1 in 10 000 births. Its clinical presentation varies widely, from asymptomatic, through involvement of only the skin, to involvement of the eye or nervous system, or widespread dissemination.

The risk of transmission from mother to baby at the time of birth is high in primary herpes infection, but the risk of infection from a mother with recurrent genital herpes is very low. Viral shedding is rare in the absence of a lesion. ‘Prophylactic’ cesarean section should not be offered to a woman with a history of herpes simplex infection who does not have clinically active herpes at the time of birth.

Clinical assessment remains the best criterion for identifying women who are shedding virus at the time of delivery. Asymptomatic shedding at delivery cannot be predicted on the basis of cultures during the pregnancy, and repeated cultures in asymptomatic women will not identify those women who are shedding asymptotically at the time of delivery.

One controlled trial has studied the effects of acyclovir given to women with a history of recurrent genital herpes. In this study, pregnant women with recurrent genital herpes (mean of three symptomatic recurrences in previous 6 months) received acyclovir 200 mg four times daily, beginning one week before the expected date of
delivery. This treatment resulted in significant reductions in maternal viral shedding at the time of delivery, symptomatic recurrences within 10 days of delivery, and use of cesarean section for herpes. There were no cases of neonatal herpes in either the treatment or the control group, and no maternal or neonatal side-effects were seen. Although these results indicate that acyclovir can be effective in reducing maternal viral shedding and symptomatic recurrences, further confirmation is required before a firm conclusion about the role of antenatal acyclovir in recurrent genital herpes can be drawn.

There have been no randomized trials to evaluate care policies for women with herpes in pregnancy, and the evidence on which these are based is weak indeed. Current recommendations are that cesarean section should be carried out if there is clinical evidence of active disease, viral shedding cannot be ruled out, and the membranes have not been ruptured for more than 4–6 h. The infant born to a woman with a history of genital herpes should be carefully monitored.

8 Bacteriuria

Significant numbers of bacteria are harbored in the urine (bacteriuria) of 3–8% of pregnant women, usually without exhibiting any symptoms, and 15–45% of untreated women with symptomless bacteriuria will develop symptomatic infections of bladder or kidney (acute cystitis or pyelonephritis). Acute cystitis and acute pyelonephritis are found in approximately 1% of pregnancies. Urinary tract infection is thus a common medical complication of pregnancy.

Culture and colony count of a single voided specimen is the best currently available form of screening for bacteriuria. Other more economical methods to screen for infection, such as the detection of urinary nitrites or microscopic analysis of a clean catch spun urine, have been suggested. These may have a role in identifying which urines should be cultured in the interests of cost-saving, but their sensitivity in pregnant women is not high enough to replace urine culture as an adequate screening test.

Recognition and treatment of asymptomatic bacteriuria in pregnancy will result in a substantially decreased risk of acute pyelonephritis and its short-term consequences to both mother and fetus. It appears to reduce the incidence of preterm birth or low birthweight as well. The mechanism through which treatment of bacteriuria leads to a reduction in preterm birth is not clear. Prevention of pyelo-
nephritis may be a factor. Treatment of bacteriuria with antibiotics may also eradicate organisms colonizing the cervix and vagina. Antibiotic treatment of bacteriuria in pregnancy has not been shown to reduce the risk of subsequent infection in the long term, but the only trial with any follow-up is small.

The available evidence from controlled trials suggests that sulphonamides, including co-trimoxazole, nitrofurantoin, ampicillin, and the first-generation cephalosporins, are equally effective in the treatment of asymptomatic bacteriuria when the bacteria are known to be susceptible.

The traditional approach to therapy for asymptomatic bacteriuria in pregnancy was continuous antibiotic treatment for the duration of pregnancy. Single-dose therapy for uncomplicated urinary tract infection in women who are not pregnant is well-established, however, and trials suggest that this may be effective for pregnant women as well. It has obvious advantages in terms of compliance, minimization of adverse effects, and financial savings. No trials of other regimens have been reported.

Symptomatic lower-tract infection in pregnancy may also respond to single-dose treatment, but there are insufficient data for this treatment to be recommended. Regular follow-up urine cultures should be obtained. Failures, relapses, and recurrences must be treated appropriately, and when infection recurs, consideration must be given to continuous treatment for the remainder of pregnancy. Recurrent infection during pregnancy may signify an underlying abnormality of the urinary tract, and these women should be further investigated after pregnancy.

9 Pyelonephritis

Pyelonephritis is diagnosed clinically by the presence of fever, flank pain, and dysuria, together with a positive urine culture. Women should be hospitalized and started on adequate antibiotic therapy after blood and urine cultures have been taken. In the absence of frank septicemia, oral therapy and intravenous therapy are associated with a similar duration of maternal fever, and the same incidences of systemic complications of sepsis and of re-admission for urinary tract infection. An aminoglycoside (with or without ampicillin) or a cephalosporin is appropriate initial treatment, as infection is probably due to *Escherichia coli*. Therapy should be adjusted when the results of susceptibility
testing are available. The use of the quinolone class of drugs should be avoided in pregnancy. Where there is concern about maternal renal function, monitoring of serum aminoglycoside levels may be warranted to minimize fetal exposure to the drug, as high levels may be associated with hearing loss in the child.

Following an episode of acute pyelonephritis, women are at risk of relapse and recurrence of infection, but the only reported randomized trial of suppressive therapy for the remainder of pregnancy failed to detect any advantage over close surveillance with cultures.

10 Rubella

Rubella (German measles) is typically a mild childhood illness. Maternal infection, occurring early in pregnancy, can lead to fetal death, low birthweight-for-gestational-age, deafness, cataracts, jaundice, purpura, hepatosplenomegaly, congenital heart disease, and mental retardation in the infant. The objective of rubella vaccination programs is to prevent fetal infection and its consequences: the congenital rubella syndrome.

The risk to the fetus of maternal infection decreases with increasing duration of pregnancy. In a prospective study, infants whose mothers had confirmed rubella at successive stages of pregnancy were followed for 2 years. No defects attributed to rubella were found in children infected after 16 weeks' gestation, while infants infected before the 11th week had significant cardiac disease and deafness.

Two approaches to rubella vaccination have been used: universal vaccination and selective vaccination. Universal vaccination of young children to interrupt transmission has led to a significant decline in reported cases of rubella and the congenital rubella syndrome. A vaccination rate of close to 100% will be needed if congenital infection is to be eliminated.

Following a rubella infection with viremia, lifelong protection against the disease usually develops. Re-infections can occur, but the majority of these are asymptomatic and detected only by a booster response in rubella-specific antibodies. Vaccination produces an overall lower antibody response than natural infection, but protection against infection can be expected in almost all vaccinated women.

The diagnosis of rubella in a pregnant woman who has been exposed to, or develops, a rubella-like infection, is often difficult. The laboratory must be provided with a detailed history, as routine screening tests
are inadequate and additional testing to detect IgM antibody is required. False-negative results can occur if the specimen is drawn too soon after exposure. The pattern of antibody response to acute infection and re-infection will vary according to the test method used, and expert consultation may be required for interpretation of data.

Pregnant women should not be given rubella vaccine, but there should be little concern if a pregnant woman is vaccinated unknowingly or if she becomes pregnant within 3 months after immunization. As rubella vaccine virus has been isolated from fetal tissue following induced abortion, the risk cannot be assumed to be zero, but receipt of rubella vaccine in pregnancy is not ordinarily an indication for termination of pregnancy. Available data suggest that the risk of teratogenicity from live rubella vaccine is virtually non-existent.

The most significant cost factors associated with rubella are related to the long-term consequences of congenital rubella. The costs of the congenital rubella syndrome far outweigh that of routine vaccination of all infants of both sexes, as well as teenage girls and postpartum rubella seronegative women.

High immunization frequency must be achieved and maintained, and all susceptible women of childbearing age should be identified and vaccinated. Prenatal screening should be carried out on all pregnant women without documented immunity, and vaccination given following childbirth, miscarriage, or termination of pregnancy, when the probability of pregnancy occurring within the next 30 days is low. Almost all vaccinated women show seroconversion, and side-effects are mild. Where follow-up cannot be assured, rubella vaccination without prior serological testing may be preferable. One-third to one-half of current cases of the congenital rubella syndrome could be prevented if postpartum vaccination programs were fully implemented.

Termination should be offered when maternal infection is diagnosed in the first 16 weeks of pregnancy. Routine use of immunoglobulins for post-exposure prophylaxis against rubella is not recommended, although it may have a role where maternal rubella occurs and termination of pregnancy is not an option.

11 Toxoplasmosis

Maternal infection with the protozoan parasite *Toxoplasma gondii* acquired during pregnancy may result in congenital infection of the infant, sometimes with serious sequelae. Individuals can be infected
only once, so a woman who is immune prior to pregnancy is not at risk of transmitting the organism to her infant.

Clinical manifestations of congenital toxoplasmosis, which consist of chorioretinitis, recurrent seizures, hydrocephalus, and intracranial calcifications, may be present at birth or appear later.

The vast majority of infections are asymptomatic in the mother, although lymphadenopathy may occur. Although asymptomatic infection can be confirmed by detection of specific IgM antibody to *Toxoplasma gondii* in serum, this test should only be performed by a reference laboratory and requires careful interpretation. Seroconversion or a fourfold rise in specific IgG antibody suggests recent infection, but a single high IgG antibody level cannot be used to confirm recent toxoplasmosis infection.

Studies on congenital toxoplasmosis have relied on serological results to identify maternal infection. Both the prevalence of seropositivity (indicative of past exposure and immunity) and the risk of acquisition during pregnancy vary among countries and even among different regions within the same country. This has been ascribed, at least in part, to different habits with respect to the handling and consumption of raw meat and the disposal of cat litter, both of which can be reservoirs of the organism. Routine screening for the condition is conducted in some countries (e.g. France and Austria) but not in many others, such as the United Kingdom, the Netherlands, New Zealand, and Australia.

The risk of transmission of toxoplasmosis from mother to baby is dependent on the stage of pregnancy at which maternal infection occurs. In one major study, the frequency of infection rose from 17%, in infants whose mothers were infected during the first trimester, to 65%, in infants whose mothers acquired the infection in the third trimester. Although the incidence of transmission from mother to fetus, based on serology, was highest in third-trimester infections, transmission in the first trimester was associated with more severe symptoms in the newborn. Severe disease occurred in 14% of first-trimester transmissions and in none of third-trimester transmissions. Some of the early infections may result in spontaneous abortions. The high frequency of neonatal clinical disease after infections early in gestation has led French investigators to recommend termination of pregnancy where feasible, and an antiprotozoan drug, spiramycin, when termination is not possible. There is no trial evidence that screening, or treatment by spiramycin alone or other combinations of drugs, does more good than harm.
When the incidence of new toxoplasmosis infection is low, the low pick-up would not justify the expense of a universal screening program. A health education program, advising pregnant woman against eating raw or undercooked meat, to wash their hands after its preparation, and to wear gloves when gardening or cleaning cat litter, might be more cost-effective. Although there is some evidence that knowledge of toxoplasmosis is increased following an educational session, there is no evidence that this knowledge is associated with changes in behavior and a reduced incidence of congenital toxoplasmosis.

Much work is still necessary to determine the true frequency of infection and the sequelae of congenital toxoplasmosis. Neither spiramycin nor pyrimethamine-sulpha are very efficacious against this parasite, and the latter agent is associated with a high frequency of side-effects in pregnant women. Trials of new antiprotozoan drugs, with potentially better efficacy and safety, are needed. Such studies will require prolonged follow-up, as some of the sequelae of fetal infections may only occur some time after birth.

12 Group B streptococcus

Group B streptococcus has become the most frequent cause of overwhelming sepsis in neonates. The early, and most serious, form of infection is characterized by rapid onset of respiratory distress, sepsis, and shock. The likelihood of disease, (approximately 2 per 1000 live births) is directly related to the density of maternal colonization and the immaturity of the infant. Infants with birthweights of less than 2500 g have a much higher overall infection rate than infants weighing 2500 g or more. Prelabor rupture of the membranes and maternal fever are also associated with a higher incidence of infection.

Attempts to prevent disease by giving antibiotics, to either all babies or those considered to be at high risk, have proved disappointing. Although the available data suggest that infant sepsis with group B streptococcus can be reduced with antibiotic prophylaxis given to the baby, such prophylaxis may be accompanied by an increase in sepsis with penicillin-resistant organisms, which may result in a higher rate of deaths from infection in the babies given antibiotic prophylaxis.

Since attempts at prophylaxis after the baby has been born may be too late, attention has focused on studies of the effectiveness of antepartum and intrapartum antibiotics. The available data show that
a course of antibiotics given during pregnancy results in only a temporary eradication of group B streptococcal carriage, with no detectable effects on infant colonization or sepsis with group B streptococcus. Treatment during pregnancy, unless continued into labor, has only a transient effect on the vaginal flora, and will not influence the rate of sepsis in the newborn.

There is no doubt that the use of intrapartum antibiotics reduces the transmission of group B streptococcus. The studies reviewed show a beneficial effect of treatment for women who are receiving comprehensive obstetrical care and are known to be colonized with group B streptococcus; but these results are not generalizable to all pregnant women. The optimal method of detecting colonization with group B streptococcus, whether by routine prenatal cultures or a rapid test at the onset of labor in high-risk patients, has not been determined. There is clear evidence that treatment should be given to high-risk colonized women, but insufficient evidence to recommend routine screening of all women for group B streptococcus during pregnancy.

It seems reasonable that a pregnant woman in preterm labor, or a woman with either intrapartum fever or prolonged rupture of membranes, should receive intrapartum antibiotics if either a rapid diagnostic test is positive or not available, although there is no evidence from controlled trials to support these recommendations. An alternative option would be a screening culture for all women at or before 35 weeks, with treatment of women with a positive culture during labor if there are other risk factors, such as preterm labor, prelabor rupture of membranes, or fever. In high-prevalence populations, it may be preferable to dispense with a preliminary screen, and treat all women with the additional risk factors during labor.

As intrapartum prophylaxis of colonized pregnant women offers the possibility of reducing the incidence of infant sepsis, rapid methods for screening women in labor are desirable. A number of such methods of rapid diagnosis of colonization have been developed and evaluated, but thus far none are adequately sensitive.

13 Conclusions

Prenatal zidovudine treatment can help to reduce transmission of HIV infection from mother to baby. Treatment with more potent antiretroviral combinations, with or without planned delivery by cesarean section, may also have benefits but these are as yet unproven.
Congenital syphilis can be largely prevented by identification and treatment of the infected mother during pregnancy. Routine screening is justified by the simplicity of the test and the effectiveness of treatment with penicillin. The value of screening for other sexually transmitted diseases will depend on the prevalence in the community, and the effectiveness of the available treatments.

There is at present no evidence to warrant routine screening for bacterial vaginosis in pregnancy, but it may be helpful in women with a past history of preterm birth.

Screening pregnant women to detect asymptomatic bacteriuria and treating the condition with antibiotics is worthwhile. The practice will reduce the incidence of pyelonephritis and probably also the incidence of preterm labor and low-birthweight infants. The cost-effectiveness of this screening will depend on the prevalence of asymptomatic bacteriuria in the population.

Pyelonephritis in pregnancy requires intensive treatment with appropriate antibiotics, usually intravenously, but oral therapy may be appropriate for selected non-bacteremic women with acute pyelonephritis in pregnancy.

A high community level of rubella immunization should be obtained, and all rubella-susceptible women of childbearing age should be identified and vaccinated. Rubella vaccination in the early postpartum period is safe and effective. This opportunity for immunization should not be missed.

The optimal method of detecting colonization with group B streptococcus is by routine prenatal cultures. Antibiotics should be given to high-risk colonized women during labor.

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