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INFECTIOUS COMPLICATIONS OF PREGNANCY

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Bishara J. Freij, MD, and John L. Sever, MD, *Guest Editors*

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Preface

BISHARA J. FREIJ
Guest Editor

JOHN L. SEVER
Guest Editor

The approaches to many infectious diseases get considerably modified when they afflict pregnant women. Certain asymptomatic or otherwise mild maternal infections can have devastating effects on the developing embryo or fetus. Our therapeutic armamentarium is sometimes restricted because of concerns over potential adverse fetal effects from drug use. The nature and frequency of an adverse outcome depends on many variables, including, among others, the specific pathogen involved, the gestational timing of infection, and maternal immune status. Parental anxiety over the well-being of the unborn child is very common following maternal infections. Establishing an accurate etiologic diagnosis is critical before counseling about the fetal and neonatal risks involved and options for intervention can be offered to the parents.

This issue of the *Clinics in Perinatology* was prepared with these considerations in mind. The first article details the routes and mechanisms of fetal and neonatal injury for a broad spectrum of infectious agents. This is followed by articles discussing various aspects of maternal, fetal, and neonatal disease caused by 17 pathogens. The selection included in this issue is intended to provide a mix of newly recognized fetal pathogens such as the human immunodeficiency virus and human parvovirus B19, common but underrecognized agents such as enteroviruses and chlamydiae, common and continuing management challenges for obstetricians and neonatologists such as herpesviruses and toxoplasmosis, as well as "old" organisms that continue to cause unnecessary maternal and fetal disease, such as syphilis, tuberculosis, and rubella.

Because of the great time and effort expended in preparing these comprehensive reviews, we are very grateful to the contributors for taking time from their busy schedules to help with this project. We also would like to thank Louise Harris for her meticulous help in preparing this issue and Mary K. Smith of the W.B. Saunders Company

for her constant support of this work. Finally, one of the editors (BJF) is also greatly indebted to Taunya Jenkins and Gary Stone for help that went well beyond the call of duty, and to Lynn M. Soban for help in focusing his attention on the more important issues and for making it all worthwhile.

We hope the readers find the articles both informative and enjoyable reading.

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Mechanisms and Pathways of Congenital Infections

*Steven L. Zeichner, MD, PhD**
and Stanley A. Plotkin, MD†

Fetal and neonatal infections range from the trivial, even inapparent, to the profoundly damaging. They may leave only serologic evidence of their passing or they may deform or kill the fetus. Although the damage done by neonatal infections undoubtedly depends on the virulence of the agent and the susceptibility of the fetus, the route through which the agent gains access to the fetus and the time in gestation when the infection occurs also influence the outcome. A review of the routes through which congenital infections reach the fetus and the mechanisms by which they cause injury may help in organizing our views of congenital infections and in understanding the pathophysiologic processes involved.[125]

Congenital infections can occur at any time from before conception up through the perinatal period. Below we consider each of the principal times during conception that congenital infections may affect the fetus and offer some representative examples of agents and their pathophysiology. We concentrate here on the mechanisms involved in infecting and damaging the fetus; we refer the reader to the following chapters on the specific infections for further details of the individual agents.

INFECTIONS BEFORE CONCEPTION

Endogenous Retroviruses

Although they have not yet been associated with human disease, endogenous retroviruses are, in a sense, the most profoundly "con-

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genital" infectious agents known (for review see reference 30). Retroviruses that have integrated stably into the genome are termed *endogenous retroviruses*. Chicken and mouse endogenous retroviruses have been the most extensively studied, but endogenous retroviruses are present in many species, including humans.[97] There are some species and populations of species in which endogenous retroviruses have not been found.[31] There may be a relatively small number of viral genomes present or up to several hundred in some strains of laboratory mice. Endogenous retroviruses are present at discrete sites on chromosomes and segregate in a mendelian fashion. The integration of an endogenous retrovirus has been associated with a stably inherited mutation in a somatic gene.[73] In experimental systems, an exogenous virus can integrate into the genome and be inherited in a stable fashion; when preimplantation mouse embryos were infected, germline transmission occurred, but when newborn mice were infected, germline transmission did not.[72]

In mouse systems, the presence of particular endogenous retroviruses has been associated with mammary tumors and leukemia[72, 102]; in humans such associations are yet to be established. Nevertheless, the observations that a virus can infect an embryo, that the virus can go on to integrate stably into the germline, segregate in apparently mendelian fashion, and then cause disease in subsequent generations is an instructive example of a congenital infection with a mode of transmission not often demonstrated in clinical practice and with potentially far-reaching effects.

INFECTIONS BEFORE IMPLANTATION

Local Processes

Although not strictly congenital infections, maternal infections prior to conception can certainly have a dramatic effect on pregnancy. The sequelae of pelvic inflammatory disease can prevent conception altogether or, if conception does occur, can lead to an increased incidence of ectopic pregnancy, with all the morbidity and mortality that implies for both mother and fetus, including such problems as hypoplastic lungs and fetal compression syndrome.

Local infections of the maternal reproductive tract present at the time of conception or implantation may harm the embryo. An endometritis might prevent implantation, and indeed chronic endometritis is one of the mechanisms hypothesized for the action of IUDs. Other local infections, for example, toxoplasma cysts or bacterial abscesses, might in theory damage either the embryo around the time of implantation or the placenta later in gestation.

Preimplantation Viral Infections

Definitive information about congenital infections during the period of gestation immediately after conception is scarce for humans.

However, some information on animal models exists. In general, the experiments demonstrate that the developmental state of the embryo has a strong effect on the outcome of infection. Heterospecific papovaviruses can infect and destroy mouse embryos in a dose-dependent fashion,[3] and the ability of the SV40 and polyoma papovaviruses to infect and destroy the embryos depends on the developmental stage of the embryo. Polyoma virus sequences can replicate in mouse embryos but not in oocytes, and the ability to replicate depends on particular DNA sequences in the viral origin of replication. These sequences appear different from those required for replication in differentiated mouse cells.[162] When the papovavirus SV40 was injected into mouse oocytes, the normally tight temporal regulation of viral gene expression did not occur.[27] These and other similar results indicate that developmentally regulated host factors can have significant effects on the ability of viruses to infect an embryo productively at a given stage of development.

Within the past few years it has become increasingly clear that DNA viruses such as the papovaviruses, adenoviruses, and herpesviruses rely on cellular regulatory systems to control the expression of the viral genes as well as to alter the expression of cellular genes to suit their own purposes. Some of these cellular regulatory systems depend strongly on the developmental state of the cell. In experiments with teratocarcinoma cells, which are cells grown in culture that share many similarities with embryonal stem cells and that can be induced to differentiate following appropriate treatment, the expression of viral genes depends on the developmental state of the cell. Undifferentiated teratocarcinoma cells contain a factor that can complement certain adenovirus mutants.[71, 130] Further, undifferentiated but not differentiated teratocarcinoma cells contain factors that bind to and increase expression from certain viral promoters that in a normal infection depend on other viral genes for their expression.[90] Findings such as these provide further evidence that the state of development can have a major influence on the course of viral infections and suggest possible mechanisms behind the clinical truism that the effect of the congenital infection on the fetus depends strongly on the time during gestation when the infection occurs.

Reoviruses can infect mouse embryos at the two-cell stage.[2, 66] The ability of the reovirus to kill the embryos depended on the serotype of virus used and the multiplicity of infection (MOI); at low MOIs a larger fraction of infected embryos survived. Interestingly, although reovirus infection occurring later in gestation appeared to be associated with congenital malformations, no congenital malformations were noted in mice born from embryos that had been experimentally infected before implantation, implying that infections at very early stages of development may produce different effects from those same infections occurring after organogenesis has begun.

Other Infections Before Implantation

The investigation and even description of infections occurring in humans before implantation are necessarily limited by ethical and

technical considerations. Thus most of our knowledge of preimplantation infections derives from animal experimental systems. Because in animal models most infections of the preimplantation embryo end in fetal wastage and not in the birth of obviously stigmatized offspring, the effects of such preimplantation fetal infections in humans must be difficult to recognize clinically.

INFECTION AFTER IMPLANTATION

The largest number of infections observed to cause significant effects in offspring occur between implantation and birth, particularly during the first trimester. It is this time, during organogenesis when infections apparently have the greatest potential for seriously disrupting the scheme of development. Some effects may be relatively nonspecific, others depend on the particular tropisms, virulence, and mechanisms of reproduction of the individual agents. As a general rule, congenital infections due to many kinds of organisms that infect the fetus between implantation and the immediate perinatal period share some common features. After the agent gains access to the mother, she becomes viremic, bacteremic, or parasitemic. Through the maternal circulation, the agent invades the placenta and then enters the fetal circulation. Fetal infection follows, with the particular organs invaded, the extent of fetal damage and the sequelae depending on the virulence and tropisms of the individual agent. In general, if the mother has developed an effective humoral immune response against a particular agent, the fetus suffers few if any harmful effects. Thus, fetal damage usually follows the infection of a mother who has had no experience with the particular agent.

Nonspecific and Indirect Effects

Some maternal infections may have profound effects on the developing fetus without the infection being transmitted to the fetus. Mothers who have chronic or debilitating infections, such as parasitic infections with a large parasite burden, may produce infants who are premature or have low birth weight.

Mothers with an acute infection may possibly give birth to babies with defects due not to the specific actions of the infectious agents, but to the actions of the infectious agents on the mother that then produce secondary negative effects on the fetus. Pyelonephritis and other urinary tract infections are associated with premature labor[78]; genital colonization with some mycoplasma species has been associated statistically with low birth weight, although the causal relationship remains obscure.[84] Chorioamnionitis also can result in preterm labor as well as cause an ascending infection of the fetus. Mothers with such diverse infectious and postinfectious processes as septic shock, disseminated intravascular coagulation, viral myocarditis, and poststreptococcal glomerulonephritis obviously run the risk of giving birth to severely affected babies.

Viral Infections

Viruses make up the largest number of infectious agents that produce significant pathology in the fetus. The damage each virus inflicts on the fetus depends on the basic biologic properties and the interactions of the virus with the developing fetus.

Rubella. Rubella is one of the best known and best investigated of the viruses causing congenital infections. Congenital rubella syndrome was recognized long ago as a classic triad: cataracts, sensorineural deafness, and congenital heart disease—largely patent ductus arteriosus and malformations of the pulmonary arterial system.[115] More recently, many other features were recognized in addition to the typical pattern of malformations[35, 141]; namely, intrauterine growth retardation, CNS disease with meningoencephalitis and secondary retardation,[36] and cataracts and retinopathy. The spectrum of congenital rubella includes as well pneumonitis[22] and bony lesions,[134] immunologic disorders,[9, 63] chromosomal anomalies,[113] hepatitis,[44] and the clinically ominous manifestations of thrombocytopenic purpura.[34] While most of the defects are recognized at birth, some, like deafness, may not be noticed until later,[122] and others, largely endocrinopathies, cataracts, and progressive panencephalitis do not develop until long after birth,[142] and, in the case of cataracts, may result from continued viral replication.

The fraction of infants born with clinical, virologic, and serologic evidence of intrauterine infection depends strongly on the time during pregnancy when the mother became infected.[103, 158] Infections during the first trimester cause fetal infection, significant defects, and spontaneous abortions much more often than those occurring later in gestation. Severe sequelae and larger abnormalities in such quantifiable characteristics as birth weight and head circumference occurred in babies infected early in pregnancy.

Fetuses become infected after their mothers become viremic. Viremic mothers apparently seed the placenta, which in turn leads to fetal viremia and infection of fetal organs. Pathologic studies of abortuses demonstrate necrosis of vascular endothelial cells in the placenta, as well as focal areas of necrosis in fetal tissues, perhaps indicating the route through which the infected placenta in turn seeds the fetal circulation. Placentas may contain virus even when the fetus does not, indicating infection of the placenta need not uniformly lead to infection of the fetus.[128, 156]

The rubella virus appears to damage the fetus through a variety of mechanisms. Rubella can result in areas of necrosis and cell death.[101, 157] It can infect vascular endothelial cells and presumably damage tissue through embolization and altered perfusion. Organs in some congenitally infected infants appear to contain decreased absolute cell number and altered cell growth patterns,[108, 129] perhaps due to persistent viral infection, since virus continues to grow in infants with congenital rubella for long periods after birth. This phenomenon is reflected in vitro, where fibroblast strains cultured from

various organs will be induced into mitotic arrest after infection with rubella virus, although the arrest may not occur for many passages, and the cells will appear otherwise normal.[124] An explanation for the induction of the mitotic arrest in vitro was suggested by the demonstration of a soluble factor produced by infected cells, which acted on uninfected cells to inhibit mitosis.[123]

Chromosomal abnormalities have been associated with congenital rubella infections, and these may contribute to altered growth.[113] There is some suggestion that autoimmune phenomena, triggered by persistent rubella infection and antigenemia, may be related to some of the late effects of congenital rubella, particularly the endocrinopathies.[22, 29, 154] A recent study showed that cultured human mesenchymal cells persistently infected with rubella grew less rapidly than control uninfected cells and exhibited less of a growth response to epidermal growth factor, probably because they internalized the epidermal growth factor less well.[164] Studies such as this may help to explain on the cellular level how such broad observations as intrauterine growth retardation and microcephaly result from the intrauterine and persistent rubella infections, although the molecular details underlying all the many manifestations of congenital rubella certainly remain obscure.

Other RNA Viruses. Although less is known regarding congenital infections with RNA viruses other than rubella, some associations have been noted. The RNA viruses other than rubella that have the most direct association with congenital infections are the enteroviruses. Serologic studies of pregnant mothers have suggested an association between maternal infections during gestation and congenital malformations. Different enteroviruses were associated with different congenital malformations.[69] In enteroviral congenital infections it has been widely assumed that the route of transmission is transplacental. This assumption largely results from the observation of a number of infants, both term and premature, with infection noted at or shortly after birth.[15, 69, 74, 81, 86, 104] In some cases pathologic evidence pointed to a longstanding process, supporting the theory of transplacental transmission.[15, 69] In other cases, virologic evidence, maternal vaginal viral cultures and infant viral cultures, as well as a lack of maternal antiviral antibody, appeared to suggest a perinatal route of transmission.[104] Other RNA viruses that have been associated with transplacental infections include measles, mumps, and western equine encephalitis.

Cytomegalovirus. Cytomegalovirus (CMV) is perhaps the most common cause of congenital infections and disease. The typical features of congenital CMV included intrauterine growth retardation, microcephaly with encephalitis and intracerebral calcifications, chorioretinitis, and sensorineural deafness. Affected infants can suffer from pneumonitis, hepatitis and hepatomegaly, splenomegaly, petechiae, and purpura. The long-term sequelae can be quite severe and depend largely on the CNS lesions and damage to the special senses; some of the long-term sequelae may not be completely apparent at

birth. On the other hand, a group of prospectively followed asymptomatic CMV infected children with normal hearing appeared to score as well on intelligence tests as a control group.[33] Mental retardation in clinically recognized congenital CMV syndrome appears to follow a bimodal distribution, with one peak of severely affected children and another peak of relatively unaffected children. Retardation was notably associated with certain clinical findings, such as chorioretinitis.[32]

Unlike with rubella, the effect on the fetus of timing of maternal infection is unclear. Several studies provide confusing if not wholly contradictory findings.[105, 111, 126, 146, 149] In one study it appeared that mothers infected early in gestation appear less likely to infect their fetuses than mothers infected later in pregnancy.[126] However, no such effect was observed in a larger prospective study.[146] In any case, it appears that fetuses which do become infected early in pregnancy stand a greater chance of developing serious sequelae.[146] In a guinea pig model, fewer of the fetuses exposed to maternal infection in the first and second trimesters were infected compared to those exposed in the third trimester, but the fetuses exposed during the early part of the pregnancy were more likely to suffer serious congenital defects.[87]

Also, as is unlike the case with rubella, mothers who have been infected with CMV and demonstrate an antibody response can become reinfected with CMV, and the reinfection can occur during pregnancy.[58, 148] Infants born to mothers who have been reinfected during pregnancy can demonstrate serologic and virologic evidence of intrauterine infection, but they are less likely to have congenital pathology than are infants whose mothers developed a primary infection during the pregnancy, implying that maternal antibody can have a protective effect on the fetus even when the fetus becomes infected.[111, 148] The birth of a severely damaged congenitally infected baby during the mother's primary infection can be followed by the birth of a subsequently conceived infant with an asymptomatic infection.[148] In animal models, however, some data indicate that female mice experimentally infected in puphood with murine CMV can later give birth to infected offspring with congenital defects typical of CMV and evidence of CMV DNA in their tissues.[14]

Although urine is cultured most frequently and provides the most reliable site for isolation, CMV has been isolated from most body fluids and tissues, including breast milk, semen, saliva, and amniotic fluid. In vitro and animal studies have shown that endometrial cells can support CMV growth[85] and that murine CMV injected directly into the uterus of pregnant mice at the time of implantation can result in fetal loss.[13] Interestingly, when mouse blastocysts were exposed in vitro to CMV and then implanted, a much smaller number of the fetuses were carried to term if the zona pellucida was removed, implying that the zona pellucida provides a mechanical barrier against CMV and perhaps other infectious agents. These observations may not be particularly relevant to the problems of human congenital infection

with CMV, since other experiments indicate that CMV will not replicate in undifferentiated teratocarcinoma cells. CMV will replicate in teratocarcinoma cells that have been stimulated to differentiate with retinoic acid, even when the retinoic acid is added shortly after the virus has entered the cells.[57] In other experiments,[88] the inability of CMV to grow in undifferentiated teratocarcinoma cells was associated with a lack of transcription of the CMV immediate early gene, a trans-acting gene required for expression of the later CMV genes, perhaps suggesting that undifferentiated cells do not possess the cellular transcriptional machinery necessary to support a productive CMV infection, or that they contain an inhibitor of CMV gene expression, which is depressed during fetal differentiation.

In any case, the pathogenesis of fetal infection appears similar to that seen in rubella. Maternal infection probably leads to maternal viremia, which in turn leads to a placental infection, which causes fetal viremia and so infection of the fetal target organs. Although some of the details of this pathway of infection are supported incompletely by data, observations such as of placental infection in the absence of evidence for fetal infection support this hypothesis.[61]

CMV appears to damage the fetus through mechanisms similar to those through which rubella works its damage. Intrauterine growth retardation may result from absolute decreases in the numbers of cells in organs of infected fetuses.[109] Some of the damage probably results from cell destruction, focal necrosis, and secondary inflammatory responses. Additional damage may result from CMV infection of the vascular endothelium, with subsequent compromise of perfusion. Certain typical features of CMV intrauterine infections, such as cerebral calcifications, appear to be late effects due to an inflammatory response to infected cells.

Infants with congenital CMV can have a number of immunologic abnormalities, some similar to those found in patients with congenital rubella, some unique. Congenitally infected infants can demonstrate increased levels of IgM and IgG, and circulating immune complexes have been detected, although the precise role of immune complex disease in congenital CMV remains unclear.[147] Congenitally infected infants have a specific defect in cell-mediated immunity.[50, 52] They have a diminished specific blastogenic response to CMV.[121] Since the intrinsic ability of mononuclear cells from congenitally infected infants to produce lymphokines[53] and the ability of cells from congenitally infected infants to present antigen[51] were not altered, the specific defect in cell-mediated immunity probably results from a defect in T helper cells. This defect in cellular immunity can take several years to become normal; the development of a normal response is associated with the end of viruria, implying that the altered cellular immune response seen in congenital CMV may contribute to continued viral replication and ongoing damage.

Other Herpesviruses. In a small fraction of mothers without prior exposure to antibodies, varicella-zoster virus can cause a serious intrauterine infection.[6, 120] Although the number of affected infants is

small, the range of clinical manifestations appears to include microcephaly and cortical atrophy, chorioretinitis, renal anomalies, and congenital or neonatal zoster. The distinctive features of congenital varicella are limb scarring and accompanying bony defects. Varicella virus fetopathy appears to occur principally with maternal first-trimester infections. Infections later in gestation seem to pose little risk to the fetus. Congenital varicella probably infects the fetus through the placenta following maternal viremia, since infants whose mothers have had a primary varicella infection appear to be at risk whereas infants of mothers with an episode of zoster during pregnancy appear not to be at risk.

Congenital infections with Epstein-Barr virus (EBV) present a relatively small problem. The seronegative rate among expectant mothers is low, on the order of a few percent, and few of the seronegative women become infected during pregnancy.[47, 91] Nevertheless, some case reports described a congenital syndrome that includes CNS deficits and hypotonia, cataracts, thrombocytopenia, monocytosis. proteinuria, and metaphysitis accompanied by persistent atypical lymphocytosis and suggestive serologic evidence of EBV infection.[56]

Herpes simplex virus (HSV) damages newborns mainly through perinatally acquired infections that will be discussed below, but HSV also can cause congenital disease. A small number of case reports and series (see refs. 70, 77, 106 for recent examples) described congenital malformations that include intrauterine growth retardation, microcephaly, hydranencephaly, chorioretinitis, microphthalmia, vesicular skin lesions, and hepatomegaly with elevated transaminases. The birth of an affected infant often followed a maternal history of primary herpes simplex infection or a history of contact during pregnancy with an infected person. Viral isolation and serologic evidence support the clinical impression in most cases.

Other DNA Viruses. Some evidence suggests that several other DNA viruses can cause congenital infection. Among these are hepatitis B (see below) and the poxviruses, vaccinia and smallpox.

Retroviruses—Human Immunodeficiency Virus. A number of retroviruses, such as the endogenous retroviruses described above, may be capable of causing congenital infection. At present clearly the most important is human immunodeficiency virus (HIV). Many children with HIV infections have acquired it from their mothers.[133] In the United States women are most commonly infected from intravenous drug use; the next most common source of infection is intercourse with a man at risk for infection.[60] HIV has been isolated from semen, and there are case reports that describe infection of women after artificial insemination with contaminated semen.[151] Minority women represent a disproportionate fraction of the total cases. Most of the cases in U.S. children have come from New York, New Jersey, Florida, and California.

In addition to an increased incidence of opportunistic infections and lymphomas, clinical features that have been reported in adults with AIDS, children with congenital AIDS are affected by certain con-

ditions not usually seen in adults.[116] Some observers have described a distinctive dysmorphic syndrome in children with congenital AIDS, including growth failure, microcephaly, and craniofacial abnormalities.[96] Children have a polyclonal hyperglobulinemia and a functional defect in humoral immunity as well. They may not make antibodies to new antigens, and they are at increased risk from life-threatening bacterial infections, such as pneumococcemia, that depend on a humoral immune response.[18] The neurologic manifestations of HIV infection that in the adult can result in dementias, meningitis, and sensory and motor deficits can, in children, also cause more subtle disease, such as developmental delay and loss of milestones.[43, 143] Children suffer from lymphocytic interstitial pneumonitis, the precise etiology of which remains unclear. One troubling difference between adult and congenital HIV infection is the clinical course. Although relatively long-term survivors have been reported, congenital HIV infection appears to be a more fulminant process than the adult disease, with relatively less of a latency phase.[133]

Although the precise mechanism of transmission in congenital HIV infection remains somewhat obscure, a few case reports provide useful clues. HIV has been cultured from a 20-week abortus conceived by a mother with positive HIV serology[75] and immunofluorescent evidence of HIV infection has been described in a 28-week-old premature infant.[89] However, transmission from an infected mother to her growing fetus occurs in only 30 to 50 per cent of pregnancies at risk.[140] The exact pathway of transmission remains speculative, but transplacental passage, through either cell-free or cell-associated virus, is likely. Substantial evidence suggests that nonsexual household contact does not transmit HIV.[49] HIV has been isolated from breast milk, however,[155] and several case reports describe the transmission of HIV to breastfed babies from mothers who were infected with HIV by transfusions after delivery.[166]

Much has been learned about the cellular and molecular biology of HIV infection, but some of those effects unique to congenital HIV infection are somewhat uncertain. The CD4 antigen appears to be the target cell surface molecule that interacts with HIV. Monoclonal antibodies to CD4 inhibit infection by HIV and infection of lymphocytes decreases expression of CD4.[83, 99] Antibodies coprecipitate CD4 and gp120, the HIV major envelope glycoprotein. CD4 is expressed in several cell types capable of being infected with HIV, and the artificial introduction of a functional gene coding for CD4 into cells that do not normally express the antigen rendered those cells susceptible to infection with HIV.[94] HIV can kill CD4-bearing cells in culture by inducing syncytium formation[46, 93] through an interaction between the HIV envelope glycoproteins and the CD4 antigen,[92, 145] although in vivo HIV may kill cells in other ways as well because few syncytia are seen in the natural infection.

Many of the clinically evident effects of HIV, both in adults and in congenitally infected children, almost certainly result from the relative absence of the CD4-bearing lymphocytes and the resulting al-

teration in cellular immunity. The humoral immune defect is also important, however, particularly in children. Several studies have shown that, apart from the effects on the CD4-bearing T lymphocytes, which have cells with largely helper and killer functions, HIV has direct effects on B cells and antibody production. Incubation of human B cells with HIV results in increased antibody production and cell proliferation.[139] Detergent-treated, noninfectious preparations of HIV can stimulate B cells to secrete immunoglobulin, whereas under similar conditions these preparations inhibit the B cells from showing a proliferative response to mitogens.[117] The stimulatory effect on immunoglobulin secretion appears to require T cells; the inhibitory effect was seen both with B cells treated with pokeweed mitogen, a T cell–dependent stimulus, and with EBV, a T cell–independent stimulus.[118]

Although most of the evidence gathered to date about the pathophysiology of HIV infection has been from in vitro studies, the mechanisms that damage the developing fetus almost certainly involve many of the same mechanisms. Direct killing of CD4-bearing cells, the creation of syncytia through the interaction of the CD4 antigen and the HIV envelope glycoprotein, and the direct stimulatory and inhibitory effects on the cells of the developing immune system probably give rise to the immune defects and some of the other features of congenital AIDS, such as lymphocytic interstitial pneumonitis. The ability of HIV to infect CD4-bearing cells in the CNS must contribute to the neurologic and developmental problems associated with congenital AIDS. Even further profound effects on the developing fetus have been hinted at by several recent experiments. Gene products from several DNA viruses can alter the expression of HIV genes,[54, 107] presumably through cellular intermediates that under normal circumstances act to regulate cellular gene expression. Inappropriate activity of such genes might well have serious effects on developing fetuses.

Bacterial Infections

Syphilis. Syphilis is the most important congenital bacterial infection with significant transmission during gestation. Despite the fact that highly effective therapy has been available for considerably more than 40 years, a significant amount of congenital syphilis continues to occur. In fact, review articles and case series over the last three decades have expressed surprise and concern that congenital syphilis still exists.[98, 136, 160, 163] The clinical manifestations are well described. Features of early congenital syphilis comprise hepatosplenomegaly and hyperbilirubinemia, pneumonitis and snuffles, skeletal abnormalities, and CSF pleocytosis with elevated protein. Although the spirochete responsible for syphilis may have caused more problems with congenital infections in the past than in the present, a spirochete whose contemporary importance is increasing, *Borrelia burgdorferi*, the causal agent of Lyme disease, has also been reported to cause congenital infections.[138] A mother who developed Lyme disease dur-

ing the first trimester gave birth to an infant with congenital heart disease, and spirochetes were present in spleen, kidneys, and bone marrow.

Although neonates may acquire syphilis through contact with a chancre during passage through the birth canal, usually congenital syphilis follows as the result of maternal spirochetemia, placental invasion, and subsequent dissemination through the fetal circulation to the fetal organs. The timing of transmission to the fetus remains somewhat controversial. Clearly syphilis can infect the fetus early in gestation because treponemes have been detected in first-trimester abortuses,[65] and some authors hold that mothers with disease early in pregnancy are more likely to infect their fetuses.[135] The timing of transmission to the fetus also depends on the developing capacities of the fetal immune system. The lesions that result from syphilis may not be due to direct tissue destruction as much as to the immunologic reaction that the fetal host mounts against the invading spirochete. Even though the spirochetes may be present early in gestation, little distinctive pathology is apparent, perhaps because fetuses early in gestation are yet not capable of mounting a full immune response.[144] Whereas immune complex deposition may cause some of the less common manifestations of congenital syphilis, glomerulopathy for example,[76] a chronic cellular inflammatory infiltrate is responsible for most of the pathology.[114] The involvement of the vascular endothelium in the inflammatory process with secondary fibrosis and scarring results in most of the long-term pathology.

Protozoan Infections

Toxoplasma gondii. Infants with congenital toxoplasmosis may display such classic findings as intrauterine growth retardation and microcephaly. They often have significant CNS disease, such as seizures and hypotonia, hydrocephaly, intracranial calcifications, microphthalmia, and chorioretinitis. Systemic manifestations include lymphadenopathy and hepatosplenomegaly, conjugated hyperbilirubinemia, and hematologic abnormalities, such as thrombocytopenia and eosinophilia.[5] Severe sequelae can occur in children with congenital toxoplasmosis, even when the infection is not apparent at birth. Retardation, seizures, chorioretinitis, and sensorineural hearing loss can take years to develop or become apparent.[161]

Congenital toxoplasmosis occurs commonly. In the United States the reported incidence of seroconversion during pregnancy is from 2 to 5 per 1000. Perhaps a third of these pregnancies result in infected infants. In some non–U.S. populations the risk of maternal infection during pregnancy is much higher.[5, 16, 37, 82, 152] In a French study, only about 40 per cent of mothers with serologic evidence of a new infection during pregnancy had babies with evidence of toxoplasmosis infection or had spontaneous abortions.[37]

The fetus appears to become infected as a result of transplacental transmission from a newly infected, parasitemic mother. The mother generally becomes infected following ingestion of oocysts distributed

in the environment in cat feces or from eating undercooked meat (largely pork and mutton) containing live tissue cysts (see ref. 153 for review). Maternal parasitemia apparently infects the placenta. Fetal parasitemia and infection of the organ systems involved in congenital toxoplasmosis follows. Toxoplasmae have been isolated from the placentas of mothers infected during pregnancy.[37] Prior maternal infection and immunity provide good protection against the fetal infection, although adults can become reinfected with Toxoplasma. Infants born to mothers with a prior history of toxoplasma infection only rarely become infected.[37, 131]

The likelihood of the fetus becoming infected and of developing a clinically significant infection depends on the period during gestation when the maternal infection occurs. Maternal infections late in gestation are more likely to infect the fetus, but infections early in gestation are more likely to damage the fetus,[37, 131] perhaps because damage to an organ at an earlier stage of development can cause more harm. This is a phenomenon observed with several other congenital infections, such as rubella and CMV.

The damage to fetal organs probably results from the deposition of tachyzooites in the various tissues and their subsequent multiplication.[131] Multiplying intracellular tachyzooites can kill individual cells, sometimes producing focal areas of necrosis and even abscesses that can later become calcified. In the brain the damage and subsequent inflammation can lead to an obstructive hydrocephalus. Extracellular tachyzooites in the tissues can incite an inflammatory response that also can damage the fetal tissues. Reports of favorable responses to treatment of congenital toxoplasmosis[5] and the observation that babies with apparently subclinical infections can go on to develop significant sequelae[161] argue that continued replication of the organism and secondary tissue destruction play a role in the development of the late effects seen in the syndrome.

Other Protozoa. Plasmodium species can cause congenital infections, although this appears to happen relatively rarely. Of interest are cases of congenital malaria that have been reported in infants born to mothers with asymptomatic infections residing in nonendemic areas.[100] A number of cases of congenital *Trypanosoma cruzi* infection have been reported.[19] In this infection too, the agent appears to spread to the placenta via the hematogenous route, invade the placenta, and gain access to the fetal circulation, resulting in a disseminated fetal infection. In some cases, placental infection without fetal infection has been observed (cited in ref. 19). The parasite appears first to invade and then to destroy the trophoblast before entering the fetal circulation.

PERINATALLY ACQUIRED CONGENITAL INFECTIONS

Birth, as pediatricians and obstetricians are all too aware, is a profoundly traumatic process. The infant is exposed to large volumes

of maternal blood and the integrity of the placenta is compromised. The fetus leaves a theoretically sterile environment and traverses a birth canal potentially colonized with many different pathogens. This circumstance leads to a distinctive group of perinatally acquired infections. Most infections transmitted to infants in the perinatal period depend on direct inoculation of newborn organs—skin, eyes, and respiratory system—with subsequent dissemination and systemic infection. This is in marked contrast to the intrauterine infections, in which the principal mode of transmission is from the maternal circulation through the placenta and on to the fetal circulation. Because of these special circumstances some useful therapeutic options are available for infants with perinatally acquired congenital infections.

Perinatal Viral Infections

Herpes Simplex Virus. Infants with neonatal herpes infection most often present with vesicular skin lesions. Other manifestations include eye disease, CNS disease with meningoencephalitis and seizures, visceral disease, and a clinical sepsis-like picture with respiratory failure, hypotension, and disseminated intravascular coagulation (DIC).[159] Newborns usually acquire a herpes simplex infection perinatally, but many case reports exist that suggest transmission *in utero* (see ref. 48 for an example). An older, nonprospective study suggests that when mothers suffer a herpes simplex infection during the first 20 weeks of pregnancy, they exhibit an increased rate of spontaneous abortion. The same study also suggested that the effect is more pronounced when the mothers suffer from a primary as opposed to a recurrent infection, although some of the cases listed as primary may in fact have been recurrent cases in which the primary infection was unrecognized. Furthermore, mothers infected during the last half of gestation have an increased risk of delivering a premature infant.[110] A more recent study also suggested an increased rate of complications for the newborn of a mother with primary infection during pregnancy. "Primary" is defined as a first clinical episode without serologic evidence of prior infection or with systemic signs and symptoms.[26] Forty per cent of the patients with primary infection had serious perinatal morbidity compared to none of the patients with "nonprimary" first episode infections. The highest risk of perinatal morbidity was noted in mothers with primary infection during the third trimester.

Infants with perinatal disease appear to acquire their infection as the result of direct contact with infected maternal tissues or fluids. Infants born through the birth canal with clinically apparent herpes lesions are at increased risk for neonatal herpes simplex, as are infants born vaginally to mothers with persistently positive genital cultures for herpes simplex. Formerly, it appeared that approximately one half of the infants born vaginally to mothers with an active infection, probably primary genital infection, become infected.[110] However, more recent studies have observed a much lower frequency of transmission.[8, 127] A significant number of babies with neonatal herpes are

born to mothers without prior history of genital herpes and negative cultures.[39] Mothers certainly can be positive by culture or histology yet not have clinical symptoms or obvious lesions on examination.[21, 110] A substantial fraction (about 35 per cent in one study) of asymptomatic American women have serologic evidence of prior type II herpes infection, indicating that they are potentially at risk of developing recurrent lesions.[21] In one prospective study, 4 per cent of asymptomatic obstetric clinic patients had positive genital herpes culture results.[21] Several studies have reported avoidance of neonatal herpes among infants born vaginally to mothers with a history of genital herpes, but with negative examination results, cultures, and cytologic studies close to the time of delivery.[20, 28, 59] Reactivation and recurrent viral shedding are fairly common during pregnancy, however. In one study[28] the mean duration of viral shedding from the cervices of pregnant women was only 4.6 days and ranged down to 1 day. Many women had recurrent viral shedding during pregnancy and a substantial fraction, 18 per cent, had recurrences less than 21 days apart. In another study,[26] the rate of recurrences was 0.3 per month. Thus, a single negative culture in a mother with a history of genital herpes does not eliminate the possibility of subsequent viral shedding and consequent risk to the newborn.

Although collected years ago, the data on cesarean deliveries and neonatal herpes further illustrate the requirement for direct contact with infected tissues or fluids. Infants born to mothers with genital herpes by cesarean section before or shortly after spontaneous rupture of membranes have a much lower risk of neonatal herpes than those born vaginally. If more than about 4 hours elapses between the time of membrane rupture and delivery, however, the risk of neonatal herpes increases, presumably because infected material ascends the birth canal during labor and reaches the fetus.[110] Reports of disseminated neonatal herpes simplex infections first becoming evident at the sites where fetal scalp monitor electrodes had been attached[80, 119] and reports of disseminated neonatal herpes simplex infections due to nosocomial exposure,[45] infected breast milk,[40] and a paternal case of oral herpes[39] all emphasize the role of direct contact with infected material.

Hepatitis B Virus. Infants infected perinatally with hepatitis B virus can develop a clinical hepatitis picture, with elevated transaminases, chronic active hepatitis, and even a fatal fulminant hepatitis. However, most newborns infected with hepatitis B are asymptomatic.[41, 42, 67] Some recover completely from the acute infection, whereas others go on to be chronic carriers. The predominant route of transmission is perinatal, rather than transplacental or postnatal. Although cases of hepatitis B with onset very early in life have been reported, most occur at several months of age, implying that the infection was transmitted around the time of birth.[7, 55] As with many other congenital infections, a new maternal infection during pregnancy, accompanied by viremia in the absence of antibody, appears

to place the fetus at increased risk of transplacental transmission. The relatively short incubation time for hepatitis seen in babies of mothers who have acute hepatitis in gestation reinforces this observation.[55] The ability of hepatitis B immune globulin and hepatitis B vaccine given soon after birth to protect the infant from disease also demonstrates the importance of perinatal transmission.[17, 150] Postnatal transmission to infants may be important in regions of the world with high rates of endemic hepatitis B.[95]

Bacterial Infections

Group B Streptococci. Group B streptococcal disease has two main patterns of clinical presentation: (1) infants affected within the first hours or days of life present with respiratory distress and signs of sepsis, and (2) late-onset disease occurs after the fifth day of life; it begins less dramatically, with lethargy, irritability, and poor feeding. Its pathologic features include meningitis.

A large fraction of pregnant women, approaching 30 per cent in some populations, carries group B streptococcus genitally or rectally.[11, 38, 68] These women are almost entirely asymptomatic. They almost certainly carry the organism for long periods and even when the organism is eliminated from their genital tracts their infected sexual partners quickly reinoculate them. About half of the infants born to mothers positive for group B streptococcus also are culture positive[68]; close to 1 per cent of these babies develop disease.[12] Important risk factors for symptomatic group B streptococcal disease in the neonate include prematurity, low birth weight, and prolonged rupture of membranes.[23] Although some newborns with early-onset group B streptococcal disease have symptoms at or shortly after birth and so presumably acquire the infection *in utero*, the well-described risk factors and the essentially asymptomatic nature of the maternal infection argue against transplacental spread of infection. In one retrospective study of placental pathology associated with early-onset group B streptococcal disease[112] over one half of the placentas examined showed evidence of chorioamnionitis. That finding correlated with prematurity and prolonged rupture of membranes. Such associations and the still-large fraction of placentas from infants with early-onset group B streptococcus without obvious pathology tend to indicate that newborns with group B streptococcus infections and symptoms in the immediate perinatal period become inoculated by organisms ascending the birth canal.

Infants with late-onset group B streptococcal disease probably become colonized during birth but do not develop an invasive infection until later. There is some evidence that the dose of group B streptococcus is important. Mothers who are "heavily colonized" appear to be more likely to give birth to a colonized infant and so to have an infant with a group B streptococcal illness.[24, 68] These observations also support the notion that newborns become colonized and infected through direct inoculation from an infected birth canal. Infants can

Table 1. *Agents Discussed*

	CLINICALLY SIGNIFICANT	TIME OF TRANSMISSION			
		Before Conception	*Before Implantation*	*Intrauterine*	*Peripartum*
Viruses					
Endogenous retroviruses	No	+ +			
Reoviruses	No		+		
Rubella	Yes			+ +	
Enteroviruses	Yes			+	
CMV	Yes			+ +	
Varicella-zoster	Yes			+	+
EBV	Maybe			+	
Herpes simplex	Yes			+	+ +
Hepatitis B	Yes			+	+ +
HIV	Yes			+ +	+*
Bacteria					
Syphilis	Yes			+ +	+
Group B streptococcus	Yes				+ +
Listeria	Yes			+ +	+ +
Parasites					
T. gondii	Yes			+ +	
T. cruzi	Yes			+	
Plasmodium sp.	Yes*			+	

+ + = Common mode of transmission.
+ = Occasional mode of transmission.
* = Rare.
* = Not fully established.

also become colonized through other sources in the environment[1] and go on to suffer symptomatic infection.

Many investigators have recognized the key role that peripartum transmission of group B streptococcus from colonized mother to unprotected newborn plays in the pathogenesis of group B streptococcal disease and have designed therapeutic interventions with that in mind. Parenteral antibiotics given to mothers who are culture positive for group B streptococcus shortly before delivery can prevent the colonization of the newborn and lessen the risk of group B streptococcal disease in infants born to those mothers.[25] However, problems with potential adverse effects (e.g., anaphylaxis) and the large number of mothers who would require treatment limit the widespread use of prophylactic antibiotics. Nevertheless, the findings of the prophylactic antibiotic studies provide additional evidence that intrapartum inoculation is the most important mode of transmission for group B streptococcus. In the distant future, immunization of mothers late in pregnancy with group B capsular polysaccharides may also prove effective.[10]

Listeria Monocytogenes. Listeria is an interesting perinatal infection because its clinical presentation shares some of the features of group B streptococcal infections, but it can infect the fetus through a different pathway (see refs. 4, 62, and 132 for recent case descriptions and reviews of earlier cases). Although Listeria has been less well studied than group B streptococcus, it is clear that Listeria also causes two distinctive patterns of disease, early- and late-onset listeriosis. Early-onset disease appears at or shortly after birth and, similar to group B streptococcus, presents as respiratory distress and sepsis. Meconium staining and aspiration appear often; the amniotic fluid often has a distinctive greenish purulence. In contrast, late-onset disease occurs 2 to 5 weeks after delivery. Babies with late-onset disease present with lethargy, irritability, feeding difficulty, and fever. Meningitis usually accompanies late-onset disease.

While early-onset group B streptococcal disease usually follows an ascending infection from the genital tract of an asymptomatic mother, early-onset listeriosis usually follows a systemic maternal infection. Women who give birth to affected infants often have a flulike syndrome with fever and pharyngitis, and in the course of such illnesses Listeria have often been recovered from maternal blood cultures. Early-onset listeriosis has been associated with premature labor and with low birth weight newborns, even in cases in which the membranes remain intact until just before delivery. In animals, Listeria often causes septic abortions. Some cases in humans, involving delivery of stillborn infants with cultures positive for Listeria, provide clear evidence of fetal infection. Liveborn infants with early-onset listeriosis often exhibit features such as hepatosplenomegaly, a distinctive petechial rash, and microabscesses in various organs that suggest that the infection had been present for some time before birth. There have been several reported cases of successful antibiotic treatment of mothers who had systemic symptoms with positive culture for Listeria and sometimes premature labor.[79, 165]

SUMMARY

Fetal and neonatal infections can occur at different times during pregnancy, from conception to birth. Infections that take place near the time of conception often destroy the zygote or embryo and only rarely leave definitive evidence. The mother can transmit the infection to her fetus through several routes, but the most likely routes are through ascending infections and through the blood. The inability of most agents to infect the early embryo probably depends largely on local barriers to the infectious agent, such as the zona pellucida. Some viruses, however, because of their systems for gene regulation of expression, can infect only embryos of certain developmental stages. Certain retroviruses can infect embryos, integrate into cellular DNA, and become part of the germline.

After implantation, most infectious agents reach the fetus hematogenously. Organisms circulating in the mother reach and infect the placenta. They then may breach the placenta, gain access to the fetal circulation, and disseminate through the fetal body. Agents with particular tropisms infect particular organs and cause particular symptom complexes. The damage done by the organisms depends largely on the gestational age of the fetus at the time of the infection. The ability of the agent to infect or damage the fetus at all often depends on whether the mother is experiencing a primary infection or has previously mounted an effective immune response. Agents harm the fetus through direct destruction of parenchymal cells, through destruction of blood vessels and resulting infarction, through continued replication in fetal and neonatal tissues, through altering the growth parameters of various fetal tissues, and through provoking autoimmune responses.

Infections that begin in the perinatal period usually infect the fetus by direct inoculation from infected foci in the birth canal or through direct contact with large amounts of infected maternal body fluids. Direct tissue destruction of the immediate sequelae of invasive infections usually causes the fetal damage from these perinatally acquired agents. The clinical features of the disease that begin in this period provide an opportunity for effective therapeutic intervention.

Understanding the routes of fetal infection and the mechanisms underlying fetal damage from infection will help in devising strategies for preventing and treating congenital infections.

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HIV in Pregnancy

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In December 1985, the Centers for Disease Control recommended that women at risk for AIDS, who were either pregnant or contemplating pregnancy, be offered testing for antibody to human immunodeficiency virus (HIV).[12] That recommendation was formally endorsed by the American College of Obstetrics and Gynecology in April of 1987.[1] As these policies are put into effect, obstetricians/gynecologists will become among the first clinicians to have to manage large numbers of asymptomatic patients found to be infected with HIV. Thus, these specialists whose previous experience with HIV in pregnancy has been limited to patients with AIDS or AIDS-relation complex (ARC) must be trained to manage the complex social, ethical, and medical aspects of HIV disease. Despite the difficulties that these policies will engender, the fact that the number of cases of congenitally acquired HIV disease soon will dwarf that of other fatal congenital infections makes implementation imperative.

This article summarizes the epidemiology of HIV in women, the interactive effects of HIV and pregnancy, and techniques for managing and counseling HIV seropositive parturients. It is hoped that this information will serve as a useful, practical management guide as obstetricians begin to encounter infected parturients.

EPIDEMIOLOGY

The extent to which women become infected with HIV depends partially on the degree to which heterosexual activity becomes a risk factor. Although intravenous drug use also poses a direct threat to women, almost three quarters of addicts are men, and that total pool of addicted women is small compared to the pool of heterosexually active women. Certain statistics would seem to suggest that hetero-

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sexual activity is of limited importance as a risk factor for acquiring AIDS. Currently, only 4 per cent of cases are due to heterosexual contact. By 1991, however, 10 per cent will be, and in 1987 27 per cent of cases among women were already acquired heterosexually. Furthermore, the distribution of AIDS cases reflect the mode of spread of the virus 5 to 10 years in the past. What is of more immediate importance are the modes of spread of the disease today.

The difference between the demography of AIDS cases and HIV infections is highlighted by the fact that whereas there are 13 cases of AIDS in males for each infection in females there are only 3 HIV infections in males for each case in females.[11] All the above information points to an increasing role of heterosexual activity in the spread of HIV to women. This increasing contribution of heterosexual transmission to HIV disease may herald a time when prenatal antibody testing will be offered routinely to all parturients since women infected with sexually transmitted diseases (STDs) may be unaware of their risk status. Some studies have in fact shown that a large percentage of infected women do not acknowledge being the members of risk groups.[33]

Currently, the profile of women and children with AIDS reflects the population of women who are either intravenous drug users or sexual contacts of intravenous drug users. Most of such patients are indigent black and Hispanic persons.

EFFECT OF PREGNANCY ON HIV DISEASE

Concerns have been voiced that pregnancy will accelerate HIV disease. These concerns are based on evidence that pregnancy alters immune status. Researchers have demonstrated decreased lymphocytic responses[19,21,24,51,54] are decreased levels of helper T cells in pregnancy.[53] Increases in morbidity and mortality from a variety of viral diseases, including influenza, varicella, hepatitis, poliomyelitis, and coxsackievirus have been reported.[11–13] The immune response to certain viruses, in particular cytomegalovirus and rubella virus, also may be impaired.[23,55] Thus, because HIV is a viral illness, the potential for a more fulminant course in pregnancy exists. Currently, however, there is little evidence of enhanced disease progression. Reports of the followup of asymptomatic pregnant women, identified because their children developed disease, reveal that at 28 to 30 months postpartum, 45 to 75 per cent had developed symptoms.[39,50] This is higher than the rates reported among antibody-positive homosexual men, intravenous drug users, and hemophiliac patients. Among those groups 13 to 34 per cent of those followed for up to 6 years have developed AIDS.[27,47] None of the pregnancy studies, however, used infected nonpregnant controls, so although the reported rates of progression are high, the difference in progression rate from homosexual males, for example, may be due to population differences, not pregnancy. Additionally, these pregnant women, all of whom transmitted disease

to their children, may represent a unique subset of infected women at heightened risk for disease progression. Some studies have shown, for example, that women with more advanced immunocompromise have a greater chance of birthing infected children. Further, progression from an asymptomatic to a symptomatic state during pregnancy has not been widely reported. Pregnancy, however, theoretically can mask HIV symptoms and modify the treatment of HIV disease. Several cases of delayed diagnosis have been reported during pregnancies.[37] Nonspecific symptoms such as fatigue may be dismissed as "normal" for parturients. Further, certain treatment modalities such as azidothymidine (AZT) may be withheld from an otherwise appropriate candidate for therapy if she is pregnant.

THE EFFECT OF HIV DISEASE ON NEONATAL OUTCOME

The major maternal concern of the HIV infected parturient is whether her child will develop HIV disease. Current estimates of risk are based on studies of the subsequent children born to women who already had infected children[39,50] and on preliminary prospective data, only reported in abstract form.[5,15,28,36,49] Scott followed children born to 20 mothers who had previously delivered infected children.[50] Sixty-five per cent of the later born children were infected. She subsequently reported on an additional 22 patients with an overall infection rate of 50 per cent.[49] We noted infection in 4 of 11 subsequently born siblings of infected children.[39] Since these data reflect transmission in a subset of seropositive mothers (those with previous infected children), it may not be applicable to all infected parturients. Preliminary prospective data based on small numbers of patients with short followup reveal neonatal infection rates in the 20 to 50 per cent range. Blanche et al. reported on the children of 56 seropositive women.[5] Thirteen apparently were infected, fourteen were uninfected, and twenty-nine were too young to be evaluated. In a subsequent description of that cohort, Griscelli noted that of 34 children over 1 year of age, 14 were infected.[28] Mendez et al. noted clinical illness among 9 of 23 children born to seropositive mothers.[36] Followup averaged only 4.4 months, however, and some of the illness seen in the children may not have been related to HIV disease. Using the new CDC Guidelines for the diagnosis of pediatric HIV disease,[10] subsequent data from the same cohort indicate illness in only 6 of 26 children of infected mothers, with 2 other children having seroconverted and the rest currently having indeterminate status (Mendez H, Willoughby A: Personal communication, 1987). Cohen et al. noted HIV infection among 3 of 13 children with positive cord antibodies.[15] Followup ranged from 3 to 16 months. Although serologic evidence of infection is not completely reliable in the neonatal period and followup has been generally short, the range of infection cited above provides some basis for counseling of infected parturients. Further research is needed to more fully define transmission rate and to de-

termine if any factors (e.g., immune status) can be identified that modify that rate.

ANTEPARTUM

If after counseling the patient elects to continue the pregnancy, the clinician must tailor the patient's antepartum care to her particular needs. The psychosocial impact of learning of HIV infection during pregnancy can be unique and overwhelming. As widespread testing in pregnancy begins, clinicians must familiarize themselves with support systems available to infected women. These support systems not only provide psychological reassurance but may be used to address ongoing patient concerns. Issues such as HIV transmission to sex partners, what constitutes safe sex, and testing of sexual contacts should be discussed. Effective birth control should be used to prevent subsequent pregnancies. For the discordant pair (positive–negative), mutual masturbation should be stressed with the mandatory use of condoms as a risk reduction measure. Repeated testing of the seronegative contact may be offered every 6 months if desired.

Because HIV is a sexually and perinatally transmitted virus, women should be screened for other organisms similarly transmitted. In addition to routine testing for gonorrhea and syphilis, the patient should be screened for Chlamydia and hepatitis. *Mycobacterium tuberculosis* should be ruled out. Furthermore, because CMV and toxoplasmosis frequently infect seropositive persons and because these organisms have perinatal significance, baseline antibody titers should be obtained to assist in maternal or neonatal diagnosis if symptoms subsequently occur.

During the antepartum period the clinicians must be wary of nonspecific symptoms that may, in other circumstances, be attributed to pregnancy per se. Fatigue and weight loss are common in early pregnancy but may be harbingers of ARC. Patients should be encouraged to report all symptoms and appropriate nutritional counseling should be instituted to maintain appropriate weight gain. Although no cofactors have been proven to affect the rate of disease progression, it seems logical to advise patients to avoid factors that may alter T4/T8 ratios (sleep deprivation, stress) or enhance viral replication in vitro (antigenic stimulus, infections).[26,57]

The treatment of opportunistic infections can be frustrating. In AIDS patients these infections tend to be less responsive to conventional antibiotics. Newer antibiotics may be required which have unknown fetal effects. Toxic reactions also may be seen more frequently in the immunosuppressed patient and prolonged treatment may be necessary. In addition, therapy may need to be modified further because of fetal concerns. Some examples follow:

Pneumocystis carinii Pneumonia

This is the most common opportunistic infection seen with AIDS.[32] The standard treatment is sulfamethoxazole-trimethoprim,

either orally or intravenously. Impaired gastrointestinal absorption in pregnancy may favor parenteral therapy. Prolonged treatment may be required because two thirds of patients still harbor the organism on bronchial biopsy after 3 weeks of therapy.[56] Nausea and vomiting may occur with treatment and can exacerbate hyperemesis gravidarum. Monitoring for drug toxicity such as rash, fever, neutropenia, thrombocytopenia, and hepatitis should be instituted. Trimethoprim crosses the placenta, producing equivalent levels in fetal and maternal serum and in amniotic fluid.[45] Although trimethoprim is a folate antagonist, case reports as well as placebo-controlled trials have not demonstrated an increase in fetal abnormalities.[16,43] One retrospective study reported on 186 pregnancies during which the mother received either placebo or trimethoprim-sulfamethoxazole and included 35 children who received the drugs in the first trimester. No increase in congenital malformations were noted.[8] Sulfonamides readily cross the placenta and the additional danger from this agent, especially close to delivery, is jaundice, which could potentially lead to kernicterus.[31] Sulfonamides compete with bilirubin for binding to plasma albumin. Some larger studies, however, have not demonstrated any deleterious effects.[3] One such study reviewed 194 pregnancies that were maintained on sulfamethoxazole. There was no greater incidence of jaundice in the infants of mothers who received sulfamethoxazole than in infants of mothers without drug treatment. Rapid renal secretion of sulfamethoxazole by the infant may be a factor in the prevention of jaundice, as well as maternal bilirubin metabolism. In sum, these drugs do not appear to be teratogenic, and the risks of *Pneumocystis carinii* pneumonia far outweigh demonstrated risks from sulfamethoxazole-trimethoprim. Pentamidine is usually reserved for treatment failures. Although experience in pregnancy is lacking, the condition of patients failing preliminary therapy is such that withholding of therapy would not be warranted, even though the likelihood of response after initial failure may be small.[41] Because pregnancy may exacerbate immunocompromise, it may be necessary to consider prophylaxis after initial therapy. One regimen would be pyrimethamine-sulfadoxine weekly. No malformations have been associated with pyrimethamine, but it is a folic acid antagonist so caution must be exercised. Investigational drugs like dapsone also may be effective. Experience in pregnancy, although limited, has not revealed an increased risk of fetal anomalies. It has been used successfully in pregnancy for dermatitis herpetiformis. Glucose-6-phosphate dehydrogenase should be measured, however, since hemolytic anemia may occur from drug treatment and the fetus may develop nonimmune hydrops. During pregnancy methemoglobin level should be monitored as methemoglobinemia may be seen with dapsone and can affect the pregnancy adversely.

Herpesviruses

Immunocompromised patients may experience more severe, prolonged, and persistent episodes of herpes simplex infection (HSV).

Such infections can have unique consequences in pregnancy. Primary infections have been associated with preterm births and abortions.[42] Delivery through a birth canal with symptomatic lesions frequently will result in serious neonatal disease, as will vaginal delivery through an asymptomatically shedding lesion, although significantly less frequently.[4] In nonpregnant AIDS patients, acyclovir can have an ameliorating effect on the duration and severity of symptoms. Acyclovir also suppresses recurrences and may have some theoretic benefit in pregnancy. The safety of acyclovir in pregnancy, however, has not been demonstrated.[2] Since lesions may be persistent, operative delivery is prudent in a patient who develops a lesion toward term. This will also allow safe postpartum initiation of acyclovir therapy. Finally, because lesions and theoretically shedding can be persistent, it should not be assumed that a patient who goes into labor several days to weeks after a positive culture is no longer shedding. Management decisions in that setting should be based on documented culture negative status.

Patients with severe disseminated herpes zoster infection respond to intravenous acyclovir and treatment during pregnancy may have to be considered. There is no information on whether neonatal transmission can be prevented with acyclovir.

Toxoplasmosis

The AIDS patient who develops focal neurologic findings, changes in sensorium, and fever must be suspected of having toxoplasmosis, a common cause of CNS symptoms among such patients. Transmission of *Toxoplasma gondii* across the placenta can occur, and if it does early in fetal life, can result in stillbirth, fetal damage, and delivery of a child with congenital toxoplasmosis.[46] Transmission rates of 14, 29, and 59 per cent may be seen in the first, second, and third trimester, respectively. These rates theoretically may be higher in the immunocompromised patient. Even though immunocompetent parturients who have been treated for toxoplasmosis have given birth to infected children, perinatal treatment appears to decrease transmission.[18] In France, where toxoplasmosis is relatively common in pregnancy serologic screening is routine. Parturients are tested early in pregnancy with regular repeat tests, if necessary, thereafter.[18] It would seem reasonable to adopt the same policy for the HIV-infected parturient. Although interpretation of serologic tests is difficult, the patient with very high titers and the seronegative patient are at particular risk. If seroconversion is noted, counseling about fetal risks should be given and if termination is not desired treatment with sulfadiazine (1 gm PO four times a day) and pyrimethamine (25–50 mg PO one time a day) administered. Spiramycin is not available in this country but has been used without demonstrable teratogenic effects. Although periumbilical cord blood sampling has been helpful in fetal diagnosis,[18] there is a theoretic risk of inoculating the fetus with maternal blood and enhancing the risk of congenital infection with HIV. Recurrence is common when treatment is discontinued. Therefore it is advisable to administer suppressive therapy after 6 to 8 weeks of full-

dose therapy for CNS disease. Preventive measures also play a role in the pregnant AIDS patient. Patients should be educated to avoid contact with cats and soil, to wash hands well, and to cook all meat throughout.

Candidiasis

Oropharyngeal candidiasis is the most common fungal infection seen in patients with AIDS. Pregnant women frequently have vaginal candidiases. This generally has limited perinatal significance with congenital moniliasis being exceedingly rare and neonatal thrush of little consequence. Recurrent maternal symptomatology (pruritus) may necessitate prophylactic courses of a topical antifungal after a therapeutic course (oral ketoconazole 400 mg PO every day for 14 days followed by ketoconazole 400 mg PO every day, 5 days per month for 6 months.)[52] Patients receiving this regimen should have monitoring of liver function. Although topical application of clotrimazole or another imidazole is effective, most develop recurrent infection when therapy is discontinued. Absorption of imidazole does occur in small amounts through the vaginal mucosa. Limited clinical studies have not demonstrated any adverse neonatal effects.

Tuberculosis

Mycobacterium tuberculosis frequently occurs in the AIDS patient. Therapy with standard antituberculous agents is effective and only minor modification during pregnancy is necessary. (See also the article by Jacobs and Abernathy in this issus.)

Antiviral Agents

Azidothymidine (AZT) is now being offered to immunologically compromised, symptomatic patients with HIV disease. Whether, it will be beneficial in the long run is not known. Its safety in pregnancy has not been tested. The few in vitro and animal studies undertaken so far however have not revealed mutagenicity nor malformation in rats at therapeutic doses.[9] Although the mode of action of the drug (inhibition of reverse transcriptase) does not pose an *a priori* risk to a fetus, other purine analogues (mercaptopurine) with different modes of action have been associated with occasional abnormalities.[7] One reason for infected patients to defer pregnancy would be to allow institution of antiviral therapy when indicated. There are no data available regarding the impact of AZT on the placental transmission rate of HIV.

Kaposi's Sarcoma

The first case of Kaposi's sarcoma in pregnancy was treated with chemotherapy.[44] Treatment of Kaposi's sarcoma, however, generally has not improved survival because most patients die of coincident opportunistic infections. The need for chemotherapy has been questioned, and its use must be individualized. The use of vinca alkaloids,

the mainstay of treatment, may present fetal concerns. More advanced disease may require treatment if respiratory compromise occurs.

INTRAPARTUM

A major focus of the intrapartum period is the prevention of nosocomial spread of HIV. Concern about this mode of transmission is based on the relatively large number of care providers exposed to the infected parturients' secretions (e.g., blood, amniotic fluid, and vaginal secretions). Recommendations for risk reduction techniques are based on a standard approach designed to prevent direct skin contact with potentially infected secretions.[25] It is most important that the infection control guidelines described below are neither limited only to those known to be HIV antibody positive, nor used as an indication for broad-based testing to "protect physicians." In endemic areas, caution must be exercised when handling secretions of all patients, not only those known to be infected. By focusing only on those patients known to be infected, a two-tiered infection control system is established that puts the clinician at risk from patients infected but not yet identified, who are therefore not being managed appropriately. Specific control measures include the use of gowns and gloves during deliveries, the use of gloves while handling the neonate as long as any maternal secretions remain, and frequent hand washing.[13,14] The added protection afforded by goggles, the use of which has been advocated, is purely speculative. Recent reports of infections of health care providers after skin contact with infected blood indicates that maximum caution is warranted.

One unique perinatal nosocomial concern involves the use of suction devices (e.g., DeLee, etc.) designed to clear the neonate's airway and operated by clinicians using mouth suction. Because secretions in the neonate's oropharynx may be infected and because clinicians occasionally get some of these secretions in their own mouth, a theoretical risk exists. Although no transmission has been documented via this route, enough concern exists to make it seem prudent to use wall or bulb suction, when possible, instead of mouth suction.

Finally, as in all medical settings, needles should never be resheathed, bent, or broken before discarding.

The obstetric management of women in labor is not altered substantially by asymptomatic infection with HIV. There is currently no evidence that mode of delivery alters transmission rates. Studies of children with AIDS or ARC have reported that many of these children were delivered by cesarean section, although few mothers were noted to have intact membranes at the time of surgery.[38] This information, coupled with descriptions of an AIDS embryopathy[35] and isolation of the virus from the thymus of neonates delivered in midpregnancy,[34] suggests that operative delivery plays a limited role at best in preventing neonatal disease. Some children, however, do not exhibit evidence of infection until several months after birth, so that peripartum

infection can theoretically occur. It seems appropriate, therefore, to avoid direct contact between the infected mother's vaginal secretions and fetal blood. Scalp blood sampling for fetal pH evaluation and scalp electrodes for monitoring the child could enhance inoculation of virus into the neonate. It would seem reasonable to rely on external monitoring so long as an interpretable tracing is obtainable.

Other concerns based on the immunologic alterations seen in HIV-infected persons include infectious morbidity and premature rupture of membranes (PROM). In a group of infected patients, identified because their infants became symptomatic, PROM appeared to be common, occurring in 18 out of 32 patients. In addition, four patients had chorioamnionitis. These patients may require more intensive fetal surveillance when PROM occurs and more aggressive use of antibiotics when chorioamnionitis occurs. Another common hematologic change in the HIV-positive patient is thrombocytopenia. The prevalence of thrombocytopenia in the HIV-positive patient may be as high as 10 per cent. The cause of the thrombocytopenia is unclear. Hypotheses have included antiplatelet antibodies and nonspecific binding by immune complexes. The presence of antiplatelet antibody could result in neonatal thrombocytopenia and affect management of labor. In addition, a lupus-like anticoagulant has been found in association with HIV infection. Mild elevations in partial thromboplastin time and bleeding time, as well as abnormal clot formation and platelet aggregation may be seen. Recurrent fetal wastage may occur with these inhibitors and may require treatment. Finally, clinical bleeding may occur with thrombocytopenia and an abnormal bleeding time, especially if operative delivery occurs. Anemia, commonly found in the HIV-infected patient, may complicate intrapartum management and necessitate blood transfusions.

POSTPARTUM

Breast milk has been implicated as a transmission mode[58] and current recommendations include proscription of breastfeeding by HIV infected mothers.[12] The actual risk that a child exposed *in utero* will not get infection during pregnancy or delivery but will from breast milk is unknown.

The risk of horizontal transmission to other household contacts, including the neonate, appears to be small. In one study there was no evidence of transmission among 29 household contacts and 90 children of index cases. Seropositivity was noted in 15 children secondary to vertical transmission.

Pediatric followup is important, and these infants should be referred to a physician who has special interest in HIV disease.

Cord blood will contain maternally produced antibody, which may be detectable for 15 months and currently have no diagnostic use regarding neonatal status. Although IgM specifically directed at HIV and HIV antigens can be identified,[29,30] the sensitivity of these tests

has not yet been shown to be high enough to make them useful, practical clinical tools.

Very little information is available regarding the postpartum course of HIV-infected women. The immediate postpartum course has not been noted to be remarkable.[38] Longer followup has revealed a high frequency of clinical illness, at least in that subset of mothers whose children develop disease. Therefore, referral to a physician capable of managing HIV disease should be ensured after delivery.

COUNSELING AND TESTING

The data presented in this article suggest that knowledge of HIV serostatus provides the parturient with information critical to her childbearing decisions and is also important for guiding prenatal and neonatal care. Thus it is appropriate to ensure that all infected women have the opportunity to access that data. Pursuant to that philosophy, and as part of public health efforts to reduce the incidence of pediatric AIDS, the CDC in 1985 recommended counseling and testing of parturients from groups at risk for HIV disease. In 1987 this recommendation was expanded to include all women living in "high prevalence" areas. This latter recommendation reflects the difficulty of identifying all infected persons once heterosexual spread becomes an important mode of transmission. Indeed studies from sentinel communities where heterosexual spread has been reported have noted a large number of infected women who do not acknowledge any risk factors. The tasks of establishing what prevalence is "high prevalence" and keeping track of a community's prevalence rate in order to know when it reaches "high prevalence" are among the problems that remain unaddressed by current testing programs. Additionally, there are many practical concerns clinicians must face when initiating counseling and testing programs in their own communities.

The diagnosis "AIDS" or even "HIV-antibody positive" carry stigma unlike any other diagnosis in modern medicine. These diagnoses have been the basis for discrimination in housing, employment, and insurance. Hence, if testing is ever to be accepted by patients, particular attention must be paid to the issue of confidentiality. The concept of confidentiality, although long accepted as a cornerstone of medical ethics, has been a somewhat elusive goal in actual practice. The confidentiality of the hospital record is partial, at best. Hospital personnel with no urgent need to know, ranging from housekeepers to medical students, have ready access to charts. Equally important, insurance companies (and employers who pay for them) have little difficulty acquiring records. Unfortunately, attempts to bypass the record and establish autonomous labeled files for test results can result in substandard medical care. Physicians who could benefit from the information may find it inaccessible when the counselor is off site. Information helpful to pediatricians in planning care for the child may be denied. Ideally, the solution would stem from a restitution of the

confidentiality of the medical record. That, coupled with statutory safeguards against discrimination based on HIV status would serve the dual purposes of providing health care workers with medically and obstetrically relevant information, and encouraging people to accept testing as a component of good care.

The counseling given to the patient should include, in addition to a discussion of the interactive risks of HIV and pregnancy, risk reduction education. The fetus is not the only person at risk from an infected parturient. Hence safe sex guidelines must be stressed. Every effort should be made to ensure that all sexual contacts of the patients are informed of their risk status. The patient should understand clearly that any sexual act involves some risk, that noninsertive sex is less risky, as is sex with an appropriately used condom with nonoxynol-9. Any other act involves an inappropriately high risk for seropositives.

THE FUTURE

Pending the development of a cure or effective vaccine, there are key aspects of HIV infection in pregnancy that need to be clarified to facilitate more appropriate management of infected parturients. Markers of relative infectivity must be identified, to determine which mother is at increased risk to birth an infected child. This would allow more individualized counseling and could identify a subset at particular jeopardy who would be more appropriate candidates for chemotherapeutic interventions (AZT, etc.) aimed at reducing viral loads and hence fetal risk of infection. The timing of viral transmission in pregnancy also needs to be determined. If it occurs in the first trimester, intervention would be more difficult than if it occurred in the third. The role of obstetric management (e.g., cesarean section, scalp electrodes, etc.) in transmission is also uncertain. Finally, the effect of pregnancy on HIV infection needs to be defined more precisely.

In the interim, obstetricians must be prepared to involve themselves in an expanding epidemic that will have a progressively greater impact on their patients. The obstetrician, lastly, must remember his or her role in preventing infection of patients in the first place by linking a disease control message to the usual birth control message.

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Herpesvirus Infections in Pregnancy: Risks to Embryo, Fetus, and Neonate

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Most persons will get infected with one or more of the human herpesviruses (herpes simplex virus types 1 and 2, cytomegalovirus, varicella-zoster virus, Epstein-Barr virus) during their lifetime. These viruses remain in the body in latent form following primary infection, only to reactivate periodically and produce recurrent disease. The clinical manifestations of human herpesvirus infections range from asymptomatic disease to severe, life-threatening illness, depending on variables such as the specific virus involved, patient's age, host immunocompetence, and whether infection is primary or recurrent in nature.

Gestational herpesvirus infections can alter the outcome of pregnancy significantly. These viruses may reach the embryo or fetus either hematogenously via the placenta, by ascension from an infected cervix, or through intimate contact between the fetus and infected cervical secretions during vaginal delivery. Invasive procedures such as fetal scalp monitoring or intrauterine transfusions are occasional sources of infection.[82] Once the virus reaches the developing embryo or fetus, a number of outcomes are possible as summarized in Table 1. This review summarizes our current understanding of the risks to the embryo, fetus, and newborn from maternal herpesvirus infections, pathogenic mechanisms of fetal abnormalities, management options, and prevention strategies.

CYTOMEGALOVIRUS

Maternal Infection

Cytomegalovirus (CMV) is a ubiquitous virus that infects most people during their lifetime. CMV acquisition rates vary inversely

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Table 1. *Potential Outcomes of Pregnancies Complicated by Maternal Herpesvirus Infections*

Resorption of the embryo
Spontaneous abortion
Stillbirth
Intrauterine growth retardation
Prematurity
Congenital malformations
Severe neonatal disease
Chronic postnatal infection
Asymptomatic neonatal infection
Uninfected healthy newborn

with socioeconomic status. Most people in developing countries become infected before they reach puberty.[136] In the United States, seroepidemiologic surveys indicate that 50 to 60 per cent of pregnant middle class women have antibodies to CMV, compared with 70 to 85 per cent of those from lower socioeconomic groups.[140] A recent study conducted in Houston on 1989 pregnant women of middle-to-upper socioeconomic status revealed that 50 per cent were seropositive for CMV.[155] Factors correlating with seropositivity in these women included nonwhite race, noncompletion of college education, being breastfed as an infant, maternal age of 30 years or older, and the presence of children 5 to 18 years of age in the home.

Of susceptible women, 2 to 2.5 per cent will acquire primary CMV infection during pregnancy, a risk comparable to that of nonpregnant women.[140] The rates of primary CMV infection are significantly higher for susceptible pregnant women from lower socioeconomic groups.[135] Seropositive women can develop recurrent disease as a result of reactivating a latent CMV infection or, less commonly, by getting reinfected by an exogenous CMV strain. Pregnant women may also shed CMV from one or more sites, including the cervix (8 per cent), the urinary tract (4 per cent), throat (2 per cent), and breast milk in the postpartum period (14 per cent).[136] CMV shedding results from recurrent infections in most of these women.[73] The rate of CMV shedding is highest for seropositive women 21 years of age or younger, in whom it approaches 35 per cent in the third trimester.[29]

Susceptible pregnant women may acquire CMV by kissing or sexual contact,[66] from their young children, especially those attending day care centers,[1,108,109] or, rarely, by blood transfusion. More than 90 per cent of primary CMV infections are asymptomatic.[107] Those who exhibit symptoms usually have a mononucleosis-like illness. Other manifestations are rare but include interstitial pneumonia, myocarditis, gastrointestinal ulcerations, aseptic meningitis, meningoencephalitis, Guillain-Barré syndrome, thrombocytopenia, and hemolytic anemia. CMV shedding from multiple sites such as saliva, tears, urine, semen, cervical secretions, and breast milk usually follows the initial

infection and may persist for prolonged periods. CMV also can become latent and reactivate periodically.

Diagnosis of active CMV infection can be achieved by isolating the virus from body fluids such as urine, saliva, cervical secretions, or buffy coat. Recovery of CMV from these sites cannot distinguish primary from recurrent infections. A number of sensitive serologic tests for measuring antibody to CMV are currently available. These include complement fixation, anticomplement immunofluorescence, indirect immunofluorescent antibody, immune adherence hemagglutination, and enzyme immunoassays.[143] ELISA is the most commonly used test in diagnostic laboratories. Demonstration of either seroconversion or a fourfold or greater rise in antibody titer usually is considered proof of a recent infection. It should be noted, however, that fourfold fluctuations in CMV antibody titers may occur in seemingly healthy seropositive persons,[156] and that CMV infections are not always accompanied by significant rises in antibody titers. The detection of CMV-specific IgM antibody serves as a useful marker for a recent primary infection.[62] This antibody may persist for 4 to 8 months following a primary infection, and problems in interpretation may arise if recurrent disease occurs within this period. Rapid diagnosis of CMV infection is also possible using either nucleic acid hybridization techniques or centrifugation culture assays.[58]

There is no specific therapy for symptomatic CMV infections at the present time. The use of the acyclic nucleoside DHPG in treating immunosuppressed patients with serious CMV infections appears promising.[34,49,124] Its use in other clinical situations has not been explored, however.

Maternofetal Transmission

Both primary and recurrent maternal CMV infection can lead to transmission of the virus to the fetus.[137] This occurs in about 40 per cent of pregnancies complicated by primary CMV infection.[140] Transmission may occur at all stages of pregnancy,[61,137] but the risk of severe congenital infection is probably higher when the infection is acquired during the first half of gestation.[135] Passage through an infected birth canal results in CMV acquisition in about half the patients, but virus excretion by these infants is not apparent before 4 to 12 weeks of age.[136]

Infants with symptomatic congenital CMV usually are born to women with primary CMV infection. Recurrent infections only rarely produce symptomatic congenital disease.[2,111] Maternal immunity to CMV does not prevent the vertical transmission of the virus but does reduce the risk of fetal damage from such infections.

Fetal Infection

One to two per cent of all newborns in the United States are infected with CMV. Of these, 10 per cent are symptomatic and the remaining 90 per cent have subclinical infection. Symptomatic infants have a mortality rate of 20 to 30 per cent, and most survivors develop

Table 2. *Clinicopathologic Abnormalities in Congenital Cytomegalovirus Infection*

TIME OF ONSET	ABNORMALITY
Newborn	Hepatomegaly, splenomegaly, hyperbilirubinemia, petechiae, purpura, microcephaly, cerebral and cerebellar atrophy, ventriculomegaly, prematurity, intrauterine growth retardation, chorioretinitis, microphthalmia, nystagmus, strabismus, cataract, thrombocytopenia, hemolytic anemia, fetal hydrops, deafness, periventricular calcifications, cardiovascular defects, interstitial pneumonia, gastrointestinal defects, osseous lesions
Late-appearing	Microcephaly, sensorineural hearing loss, mental retardation, optic atrophy, chorioretinitis, hypotonia, spasticity, dental defects

long-term serious sequelae such as hearing loss, mental retardation, and visual impairment. In infants asymptomatic at birth, serious sequelae such as hearing loss or ocular abnormalities develop in 5 to 15 per cent by 2 years of age.[140]

CMV infection may cause congenital abnormalities by interfering with organogenesis early in pregnancy or by infecting fully formed tissues later in gestation.[70] Evidence linking CMV infections in pregnancy with abortions or miscarriages is inconclusive. A recent prospective British study documented a sevenfold higher rate of fetal loss in women with primary CMV infection in early pregnancy compared to that of controls,[61] whereas a comparable study from Birmingham, Alabama, found the rate of fetal loss to be the same for women with primary CMV infection in early pregnancy, seropositive women, or women who remained seronegative during pregnancy.[135]

The clinical features of congenital CMV are summarized in Table 2. Enlargement of both liver and spleen are the most common clinical findings and are believed to represent a reticuloendothelial response to chronic CMV infection.[70] Hyperbilirubinemia may be transient or persistent and occasionally sufficiently elevated as to require exchange transfusion. Platelet counts are low in most patients and may result in a petechial rash.

Microcephaly is present in more than half of all symptomatic patients but is almost nonexistent in those with subclinical infection.[4] It is commonly associated with cerebral calcifications, which are usually periventricular in distribution. Chorioretinitis is the most frequent ocular abnormality followed by optic atrophy.[121] Other eye abnormalities that are occasionally present include microphthalmia, cloudy cornea, cataract, optic nerve hypoplasia, nystagmus, and strabismus. Chorioretinitis may be a late-appearing manifestation of asymptomatic congenital CMV in about 2 per cent of patients. Ocular abnormalities are commonly found in those with cerebral calcifications.

Unilateral or bilateral sensorineural hearing loss that can be mild

or profound is common in congenitally infected infants. It develops in about 30 per cent of those symptomatic at birth and in 8 to 13 per cent of infants with subclinical congenital infections.[4,69] In contrast, hearing loss is not a problem in infants with postnatally acquired CMV infections.[86]

Intellectual impairment is present in a large portion of patients with symptomatic congenital disease.[4,36] A small number of infants with subclinical CMV infections at birth may develop mental deficits or behavioral disorders, but this is very unlikely in the absence of other neurologic deficits such as hearing impairment.[35,110]

A variety of malformations have been described in infants with congenital CMV infections, but these probably reflect associations rather than true cause-and-effect relationships.[70] Cardiac defects include atrial and ventricular septal defects, anomalous venous return, tetralogy of Fallot, and congenital mitral stenosis. Musculoskeletal defects may include inguinal hernia, hip dislocation, clubfoot, and diastasis recti. Gastrointestinal defects may include biliary atresia, esophageal, gastric, or intestinal ulcers, esophageal atresia, megacolon, and omphalocele. Hypospadias has been described in a few patients. None of these anomalies are common, and many may represent a chance occurrence of an abnormality in newborns affected with a relatively common congenital infection.

Dental defects are common in patients with symptomatic (40 per cent) and asymptomatic (5 per cent) congenital CMV infections.[139] The defects are more severe in those with symptomatic disease at birth. The teeth have generalized yellowish discoloration and the enamel is opaque and hypocalcified and may sometimes be absent. Dental caries is also common.

The diagnosis of congenital CMV infection is best established by isolating the virus from urine, saliva, or other body fluids within the first 2 weeks of life. Viral isolation at a later time may represent either congenital or perinatal infection. Symptomatic newborns shed larger quantities of CMV than those with subclinical infections, and their cultures may become positive within 1 to 2 days. Infants with lower urinary CMV titers may require as long as 6 weeks before CMV cytopathology in tissue cultures can be detected. Immunofluorescent staining of cells after 24 hours of culture may provide a more rapid diagnosis in some instances. More rapid detection of urinary CMV can be achieved by electron microscopy, ELISA for CMV-specific antigens or antibodies, and DNA hybridization, but these methods are not readily available and not as sensitive as viral cultures.[103,133,138] Serologic diagnosis of congenital CMV can be difficult. Detection of CMV-specific IgM antibodies by ELISA or radioimmunoassay is useful, but these test results may be falsely negative or positive. It recently has been suggested that the serologic diagnosis of congenital CMV infection can be enhanced by simultaneous measurements of CMV-specific IgM and IgE antibodies by ELISA.[104] IgG antibodies cross the placenta, and consequently detection of CMV-specific IgG antibodies is not helpful. Maternally derived antibodies disappear within

a few months. Persistence of elevated anti-CMV titers in serial serum samples therefore confirms CMV infection. This method, however, cannot distinguish infants congenitally infected from those who acquired the virus in the perinatal period.

There is no effective therapy for congenital CMV. A variety of agents have been tried, including cytosine arabinoside, adenine arabinoside, acyclovir, leukocyte interferon, and transfer factor, but none has proved useful.

Prevention

There are no set guidelines for the prevention of CMV infections in pregnancy. Routine serologic screening of pregnant women is expensive and does not provide the same amount of useful information as does rubella screening. Maternal CMV antibodies do not prevent recurrent infections nor transplacental passage of the virus. The fetal infection produced is only rarely severe, however. It is also difficult for susceptible pregnant women to reduce their risk of exposure to CMV since the virus is endemic and most infected persons are asymptomatic. If these women work closely with infants and children as in hospitals or schools, they should be encouraged to practice good personal hygiene, especially handwashing. It is not known whether transferring these women to areas with less contact with infants and children would actually reduce their overall risk of acquiring a primary CMV infection.[80]

Termination of pregnancy is one option for women who develop primary CMV infection. These patients should be informed that their risk of delivering an infant with symptomatic congenital CMV infection is only about 5 per cent. Prenatal diagnosis by recovering the virus from amniotic fluid is of limited value. If CMV is isolated, it indicates fetal infection but does not necessarily imply severe disease. On the other hand, failure to recover the virus from amniotic fluid does not rule out the possibility of fetal infection.[136]

Stern and colleagues[144] recently studied the lymphocyte transformation responses to CMV antigen of 14 pregnant women who had acquired a primary CMV infection. These investigators found that intrauterine transmission of CMV did not occur in eight women with positive responses, but that four of six women with negative responses delivered congenitally infected, but asymptomatic, neonates. These data, if confirmed after studying a larger number of women, suggest that it may be possible to predict with reasonable accuracy whether an intrauterine fetal CMV infection had occurred but not whether it had caused a severe or otherwise asymptomatic infection.

Several live and killed CMV vaccines are currently under investigation, but none is available for clinical use.[112]

HERPES SIMPLEX VIRUS

Maternal Infection

Herpes simplex virus (HSV) infections are common and exist worldwide. The multitude of human HSV strains that exist in the gen-

eral population can be grouped into two serologic subtypes, HSV-1 and HSV-2. These subtypes can be distinguished by several serologic tests, including neutralization assay, radioimmunoassay, and ELISA, but not the standard complement fixation antibody assay. Because the antibody response to HSV is usually directed against type-common rather than type-specific antigenic determinants, however, it is often difficult to detect antibodies to one subtype in patients with prior antibodies to the other subtype.[39]

HSV can cause a variety of infections, including gingivostomatitis, pharyngitis, genital herpes, herpetic whitlow, keratitis, chorioretinitis, encephalitis, esophagitis, pneumonia, hepatitis, and severe neonatal disease.[40] Asymptomatic infections are also common. Seroepidemiologic surveys show that the prevalence of antibodies to HSV increases with age and is higher in groups with a lower socioeconomic status.

The most common clinical manifestations of primary HSV-1 infections are gingivostomatitis and pharyngitis, but the virus may cause from 7 to 50 per cent of primary genital herpes infections as well.[145] Recurrent episodes of herpes labialis are very common. Both primary and recurrent HSV-1 infections may be subclinical, and the virus may be shed from the pharynx in as many as 5 per cent of asymptomatic healthy persons.

The most common infection caused by HSV-2 is genital herpes. HSV-2 antibodies are usually not detected before adolescence and their prevalence depends on age, sexual activity, and socioeconomic status. In seroepidemiologic surveys of women attending obstetrical clinics in Seattle, antibodies to HSV-2 were found in 46 and 23 per cent of urban women from lower and middle socioeconomic classes, respectively.[39] In contrast, these antibodies may be detected in about 80 per cent of female prostitutes and only 3 per cent of nuns.

Most patients with primary genital herpes have local and systemic manifestations while those with recurrent infections have a milder illness. Most herpes infections during pregnancy represent recurrent disease. Asymptomatic shedding of HSV occurs in 0.2 to 7.4 per cent of pregnant women[141] and in 0.2 to 4 per cent of those at or near term.[37] Recurrent genital HSV infection is due to HSV-2 in most patients.[40] The recurrence rate increases as pregnancy advances[23] and the likelihood of reactivation of genital HSV infection is higher for HSV-2 than HSV-1.[87]

Diagnosis of HSV infections is best established by recovering the virus from tissue cultures of clinical specimens. If large quantities of virus are present, a positive result can be obtained within 1 to 2 days. Direct detection of HSV antigens in exfoliated cells using indirect immunofluorescence or ELISA is also possible. These techniques are not as sensitive and specific as tissue cultures but are more rapid. Cell culture for 24 hours followed by staining with labeled antibodies to HSV is another rapid diagnostic method with good sensitivity and specificity. Serologic tests are usually of limited value. They can be used to document a primary HSV infection by demonstrating seroconversion or detection of HSV-specific IgM antibodies. Serology is not helpful in recurrent infections. HSV typing can be performed

using restriction endonuclease analysis or type-specific monoclonal antibodies.[145]

Acyclovir is the drug of choice for primary and symptomatic recurrent genital HSV infections, but its use in pregnancy is not approved. Pregnant women with disseminated HSV infections should be treated with acyclovir, however, since this condition carries a 50 per cent or greater risk of death for the mother or her fetus. Fetal infection may still occur even with maternal antiviral therapy.[17] Transplacental passage of acyclovir has been demonstrated,[60] but no adverse fetal effects related to its use have been observed thus far in the few women treated parenterally with this drug during pregnancy.[43,67,152] Data on the safety of oral and topical acyclovir formulations when used during pregnancy are few.[22,118] Acyclovir has recently been shown to be teratogenic in rats[142] and can accumulate in human breast milk.[91]

Maternofetal Transmission

Although most neonatal HSV infections are the result of virus acquisition during passage through the birth canal, transplacental transmission occurs with serious consequences to the developing fetus. Primary HSV infections during the first half of pregnancy are associated with an increased frequency of spontaneous abortions and stillbirths.[141] A number of cases of congenital malformations associated with primary maternal HSV infection during the first trimester of pregnancy have been reported.[28,53,71,75,83,100,115,132,147] These defects are summarized in Table 3. It is unclear whether the incidence of premature onset of labor is increased in pregnancies complicated by maternal herpes, but about 40 per cent of patients with neonatal herpes are born before the 36th week of gestation.[162]

The frequency with which intrapartum transmission occurs is not known with certainty, but several factors are associated with an increased risk of HSV acquisition by newborns. These include maternal primary infections, which are associated with the excretion of higher virus titers and for longer periods when compared with recurrent infections, cervical HSV infection, multiple lesions, prematurity, prolonged rupture of membranes, intrauterine instrumentation as with scalp electrodes, and, possibly, absent or low titers of transplacentally acquired neutralizing anti-HSV IgG antibodies. Various estimates place the risk of transmission of HSV to newborns at about 40 to 50 per cent for mothers with primary herpes[38,162] and about 5 per cent for those with recurrent infections.[18]

Postpartum transmission of HSV to neonates has been documented but is infrequent.[65,94,146] The resultant infections are comparable in severity to those that follow intrapartum acquisition of HSV.

Fetal and Neonatal Infections

HSV infections occur in an estimated 1 to 6 newborns per 10,000 deliveries per year.[141,162] Infections may be localized to one body site or disseminated with involvement of multiple organs. Subclinical in-

Table 3. *Clinicopathologic Abnormalities in Neonatal Herpes Simplex Virus Infections*

TIME OF VIRUS TRANSMISSION	ABNORMALITY
In utero	Skin vesicles, cutaneous scars, cutaneous calcifications, absence of scalp skin, microcephaly, cerebral atrophy, hydranencephaly, cerebral and cerebellar necrosis, intracranial calcifications, hepatosplenomegaly, chorioretinitis, microphthalmia, keratoconjunctivitis, cataract, retinal dysplasia, short digits, bone abnormalities
Intrapartum or postpartum Acute infection	Vesicular rash, keratoconjunctivitis, chorioretinitis, pneumonia, hepatitis, disseminated intravascular coagulation, seizures, shock, poor feeding, temperature instability, bulging fontanelle
Postinfectious complications	Microcephaly, hydranencephaly, porencephalic cysts, seizures, psychomotor retardation, learning disabilities, blindness, spasticity, recurrent mucocutaneous herpes, hearing defects

fections with HSV are very rare. It is not known why some patients develop localized disease only whereas others suffer from a severe and frequently fatal illness. Both humoral and cellular immune mechanisms appear important in preventing initial HSV infections or limiting its spread.[102,166] Several potential immune deficiencies such as lack of transplacentally acquired anti-HSV antibodies or reduced natural killer cytotoxicity may impair a neonate's capacity to protect itself from HSV infection.

Transplacental transmission of HSV with resultant fetal infection occurs but appears to be infrequent based on the limited number of published case reports.[13,28,33,53,71,75,79,83,100,115,126,132,147] Many cases probably go unrecognized, whereas in other instances the fetus may develop a severe disseminated *in utero* infection that results in its demise, which manifests clinically as a spontaneous abortion or a stillbirth. Infants infected *in utero* have disease manifestations at birth, and the defects principally involve the skin, eyes, and central nervous system (Table 3). Most of the reported cases have been associated with primary maternal genital herpes during the first trimester of pregnancy, but this syndrome has also been noted following primary infection in the third trimester and, rarely, following recurrent disease during the first trimester. Most cases have been caused by HSV-2.[54] Significant long-term neurologic sequelae are present in patients who survive beyond the neonatal period.

Neonatal infections resulting from the intrapartum acquisition of HSV may be either localized or disseminated in nature.[102] Localized

infections involving the skin, eyes, or oral cavity usually manifest at about 10 to 11 days of age and account for approximately 20 per cent of all cases of neonatal herpes.[162] Skin lesions may vary from a few discrete vesicles to large bullous lesions, and in some patients the lesions denude the affected skin. Recurrent mucocutaneous herpes at the same or different body sites will develop in these infants. Ulcerative mouth lesions with or without cutaneous involvement may be noted in other neonates. Ocular manifestations include keratoconjunctivitis and chorioretinitis. About 25 per cent of this group of infants will subsequently develop neurologic abnormalities, although they had no evidence of central nervous system involvement in the neonatal period.[162]

A second group of infants composing about a third of all neonatal herpes patients will have localized central nervous system involvement with or without skin, eye, or mouth lesions. These infants are usually initially seen at 15 to 17 days of age, and a third of them will have no herpetic skin lesions. The mortality rate is about 17 per cent but may be as high as 50 per cent in untreated patients. Forty per cent of survivors will have long-term neurologic sequelae such as psychomotor retardation (Table 3).

Infants with disseminated HSV infection account for at least half of all neonatal herpes patients. These patients usually present at 9 to 11 days of age. Multiple organs are usually involved, including the liver, lungs, adrenal glands, gastrointestinal tract, kidney, pancreas, and heart.[102] Central nervous system involvement is present in about two thirds of these patients. Without antiviral therapy, 80 per cent or more will die and most survivors will have serious neurologic sequelae.[162] The mortality rate is reduced to 15 to 20 per cent with appropriate therapy, but about 40 to 55 per cent of survivors will still suffer long-term neurologic impairment.[161]

At least 20 per cent of all newborns with localized central nervous system or disseminated HSV infection have no skin involvement, thereby making a clinical diagnosis difficult.[9,162] A high index of suspicion is essential because the signs and symptoms may closely resemble those seen with other neonatal bacterial or viral infections.

Sullivan-Bolyai and colleagues[147] reviewed 42 consecutive cases of neonatal HSV infections seen in Seattle between 1965 and 1984 and found that the first clinical signs and symptoms of disease developed within the first week of life in 67 per cent of patients, during the second week in 16 per cent, and during the third week in 14 per cent. However, the average length of time between onset of disease to diagnosis was 5 days and, surprisingly, this was similar for patients with or without visible mucocutaneous lesions on admission. In another study, the mean time from onset to diagnosis was about 6.5 days for 54 neonates with this infection.[164] Infants with longer durations of disease prior to initiation of antiviral therapy usually have a worse outcome than those treated early in the course of their illness.[164]

Neonatal HSV infections are best diagnosed by isolating the virus from one or more body sites. If a vesicular rash is present, lesion

scrapings should be cultured. HSV can be recovered from 25 to 40 per cent of cerebrospinal fluid specimens obtained from infants with central nervous system involvement. Cultures of feces, urine, throat, nasopharynx, conjunctiva, and blood may yield the virus in some patients. Virus typing is not necessary for therapeutic or prognostic purposes. Serology is not usually helpful in diagnosing neonatal HSV infection. In patients with skin vesicles, a Tzanck smear of cellular material obtained by scraping the base and periphery of the lesions provides a rapid presumptive diagnosis of herpesvirus infection if intranuclear inclusions or multinucleated giant cells are seen.[131] This test is limited by its high false-negative result rates especially when the scrapings are obtained from older lesions. A positive smear indicates herpes simplex or varicella-zoster virus. Detection of viral antigens in tissue specimens using HSV-specific immunofluorescent monoclonal or polyclonal antibodies is also useful.

Antiviral therapy with vidarabine or acyclovir is beneficial in reducing both morbidity and mortality of neonatal HSV infections. The therapeutic benefits of both drugs are very comparable.[161] These infants frequently require vigorous supportive measures. Isolation of these infants is an important infection control measure that minimizes the risk of nosocomial transmission of this virus.

Prevention

Measures currently employed in obstetric practice for the prevention of neonatal HSV infections involve the identification of women at high risk for genital herpes, monitoring them with weekly viral cultures in the last trimester of pregnancy, and delivering their infants by cesarean section if they are found to be shedding HSV at or near the time of delivery. This approach is based on the premise that neonatal disease can be prevented if contact with and acquisition of HSV during passage through an infected birth canal can be avoided. This strategy is effective in preventing some cases of neonatal herpes but has several shortcomings.

Screening all pregnant women for genital herpes just prior to term is impractical because of the poor yield expected. Targeting high-risk groups such as women with a history of genital herpes or those whose sexual partners have a history of this infection would improve the yield. Limitations of this selective screening process are that both primary and recurrent genital herpes may be asymptomatic and that about 70 per cent of newborns who develop HSV infections are born to mothers who are asymptomatic at the time of delivery. About two thirds of these asymptomatic mothers have no history of herpetic infections themselves, nor do their sexual partners.[163]

Monitoring women at high risk with viral cultures usually is started during the last 4 to 8 weeks of gestation. Women are allowed to deliver vaginally if their last one or two culture results prior to delivery are negative and there are no symptoms or visible lesions on examination. This approach has numerous limitations. About 15 per cent of neonates with HSV infections are born between 28 and 32

weeks of gestation.[18] A single genital sample will not identify all HSV-positive women if there are no visible lesions present. The length of time available to isolate HSV from tissue cultures may not be sufficient if the interval between sampling and onset of labor is short. The use of Papanicolaou smears to screen women at the time of delivery has been suggested, but this technique frequently is associated with both false-negative and false-positive results, thereby limiting its usefulness. An additional problem with weekly viral cultures is that women whose last culture results were positive may have stopped shedding virus by the time of delivery and, conversely, those whose last culture results were negative may subsequently reactivate and shed HSV at delivery. Binkin and colleagues[18] have estimated that weekly viral cultures for women with recurrent genital herpes would diagnose only a fourth of those with asymptomatic infection at delivery and that the cost of such a screening program would be about $2,000,000 per case of neonatal HSV infection that is prevented.

The inability of antepartum maternal viral cultures to correctly identify women shedding HSV at onset of labor was well documented in a recent prospective study of 414 pregnant women with a history of recurrent genital HSV infection.[8] In this study, 14 per cent had clinical recurrences of HSV infection at delivery. Of 302 asymptomatic women during their last week of pregnancy, four (1.3 per cent) were shedding HSV. Three of these four women remained asymptomatic and stopped shedding HSV by the time of delivery while the fourth went on to have symptoms of recurrent disease. Five (1.4 per cent) of 354 asymptomatic women at onset of labor were shedding the virus. However, none of these five women had had asymptomatic shedding of HSV during the last four weeks of their pregnancy. In addition, five neonates were delivered vaginally to women shedding HSV at onset of labor, but none developed disease. In a subsequent study, Prober and colleagues[113] found that none of 34 infants born to mothers with recurrent genital HSV infection acquired an infection after exposure to HSV-2 at the time of vaginal delivery. In view of the limitations of antepartum monitoring, women with a history of recurrent genital herpes who are asymptomatic at onset of labor and have no suspicious lesions on examination should be allowed to deliver vaginally.[8,23]

Cesarean section is recommended for women with signs or symptoms suggestive of HSV infection at the onset of labor. This method is most effective if the fetal membranes have been ruptured for 4 hours or less prior to surgery. Cesarean section should not be performed if the membranes have been ruptured for 12 or more hours, since the risk to the neonate is probably the same if delivered vaginally. Women with membranes ruptured for 4 to 12 hours usually are delivered by cesarean section, although the benefits of this approach are not well defined.

Cesarean sections cannot prevent cases that result from the transplacental transmission of HSV to the fetus. Women who develop genital herpes during pregnancy, especially those with primary infections in the first trimester, should be informed that they are at increased

risk for spontaneous abortion or stillbirth and that there is a small risk of congenital defects that cannot be quantitated at present. In addition, perinatal morbidity has been observed in approximately 40 per cent of infants born to women with primary genital HSV during pregnancy.[25] Isolating the virus from amniotic fluid obtained by amniocentesis is uncommon and does not necessarily indicate fetal infection.[167] Therapeutic abortions are not recommended for women with genital herpes during pregnancy.

Infants delivered through an infected birth canal should be isolated for the purpose of protecting other infants in the nursery. Cultures of exposed mucous membranes such as eyes and nasopharynx should be obtained at 24 to 48 hours of age. Cultures obtained at an earlier time may represent transient contamination if positive. If any of the cultures obtained are positive for HSV, antiviral therapy should be initiated even in asymptomatic neonates.[162]

A number of live and inactivated herpes vaccines are currently under investigation.[40] Ideally, prevention of neonatal HSV infection can best be achieved by immunizing susceptible seronegative women with a vaccine that prevents infection and the establishment of viral latency or blocks its reactivation. Such a vaccine is unavailable at the present time.

VARICELLA-ZOSTER VIRUS

Maternal Infection

Varicella-zoster virus (VZV) is ubiquitous and infects most people during their lifetime. VZV infections may be asymptomatic or manifest as varicella (chickenpox) or zoster (shingles). About 95 per cent of women of childbearing age in the United States have serologic evidence of past VZV infection. The proportion of seropositive women may be much lower in those from tropical or semitropical countries.[159]

Varicella is a highly contagious and usually benign disease of childhood. Children younger than 15 years of age account for over 90 per cent of cases. Fewer than 2 per cent of reported cases occur in persons 20 years of age or older.[27] The estimated incidence of gestational varicella is one to seven per 10,000 pregnancies.[123,141] Zoster results from reactivation of latent VZV and is more commonly encountered in the elderly or immunocompromised patients. Its incidence in pregnancy is not known but appears to be lower than that of varicella. One estimate places the incidence at about 0.5 per 10,000 pregnancies.[123]

It is estimated that less than 5 per cent of primary VZV infections are asymptomatic.[116] Varicella usually manifests 10 to 20 days following exposure of susceptible persons to VZV. The illness is characterized by fever, malaise, and a pruritic rash. The rash is primarily truncal in distribution and is characterized by crops of maculopapules that rapidly progress to form vesicles that eventually crust over. Newer

lesions continue to appear for 3 to 5 days leading to the typical finding of lesions in various stages of development. Complications include pneumonia, encephalitis, arthritis, bacterial cellulitis, and a variety of bleeding manifestations. The risk of developing complications from varicella in otherwise normal adults may be up to 25-fold greater than that for normal children.[27] Pregnancy does not seem to further increase this risk. Immunity following varicella is long-lasting.

Zoster is characterized by pain localized to the area of distribution of one or more sensory nerve roots. The skin lesions are unilateral in most patients and follow the same evolutionary pattern as those of varicella but remain localized to the radicular lines.

The diagnosis of varicella or zoster usually is based on the clinical findings only and laboratory confirmation is seldom needed. The virus can be isolated from vesicular fluid by inoculating freshly collected specimens onto human diploid cell lines. VZV-specific antigens can be detected in vesicular fluid by countercurrent immunoelectrophoresis or by immunofluorescence staining of smears of cell scrapings collected from the base of fresh vesicles.[47]

Several serologic assays are currently available for the detection of antibodies to VZV. These include complement fixation (CF), neutralization, indirect hemagglutination, immune adherence hemagglutination (IAHA), fluorescent antibody against membrane antigen (FAMA), and enzyme-linked immunosorbent assay (ELISA). These tests can be used to diagnose VZV infections or to determine the susceptibility status of a person.

CF antibodies develop within 10 days after onset of varicella and reach a peak by 2 to 3 weeks. These antibodies appear earlier in zoster. CF antibodies tend to disappear with time and by 1 year after infection about two thirds of persons do not have detectable antibody titers. This test is also insensitive compared with FAMA or ELISA. FAMA is more sensitive but more difficult to perform and is not readily available. ELISA is being increasingly used for measuring antibodies to VZV.

Two serum samples collected 1 to 2 weeks apart can provide a retrospective diagnosis of VZV infection if a fourfold or greater rise in antibody titer is demonstrated. If the first sample is collected late in the course of the illness, a single high titer indicates a recent primary or a reactivated VZV infection.

It is essential to be cautious in interpreting serologic data. Up to one third of persons with a prior VZV infection will have an antibody titer rise if they develop a primary herpes simplex virus infection.[122] It is therefore important to document the lack of an antibody titer rise to herpes simplex virus before making a final diagnosis.

Detection of VZV-specific IgM antibodies can be used to document a recent infection with this virus. The antibody can be detected for several weeks following varicella. It may also be present for a brief period following zoster. False-positive results may be encountered in patients positive for rheumatoid factor.

For uncomplicated varicella, symptomatic treatment with anti-

pruritics and cleansing of lesions is adequate. Analgesics are needed for pain control in zoster. Antiviral agents such as acyclovir are used in immunosuppressed patients[125,153] but are not indicated for otherwise normal adults. Pregnant women should not be treated with this drug unless they develop life-threatening primary varicella pneumonia.[89] Acyclovir is not useful for varicella encephalitis. The use of varicella-zoster immune globulin (VZIG) in treating varicella is of no benefit.

Maternofetal Transmission

Several lines of evidence support the concept that maternofetal VZV transmission occurs primarily via the transplacental route. Garcia noted several necrotic foci in the placenta from a spontaneous abortion of a pregnancy complicated by varicella in the fourth month of gestation.[56] Congenital malformations following infection in the first half of pregnancy are infrequent but provide further support for the notion of transplacental fetal VZV acquisition and infection, although attempts at isolating the virus from these infants have been unsuccessful.[26]

Meyers estimated that about one fourth of newborns delivered to mothers who contract varicella during the last 3 weeks of pregnancy will develop clinical infection.[98] In a recent prospective study, Paryani and Arvin used several clinical and immunologic criteria to document intrauterine transmission of VZV in 43 pregnancies complicated by varicella and 14 others complicated by herpes zoster.[106] These criteria included the presence of malformations consistent with the congenital varicella syndrome, acute varicella of the newborn, detection of VZV-specific IgM in the neonatal period, specific lymphocyte transformation to VZV antigen, persistence of anti-VZV IgG antibodies, and the occurrence of zoster in infancy. The rate of intrauterine transmission was 24 per cent following maternal varicella and none following maternal herpes zoster.

Fetal Infection

Gestational varicella is not associated with an increased incidence of prematurity[106,128] or fetal death.[129] Chromosomal abnormalities have been shown to occur following VZV infections in both experimentally infected human diploid fibroblasts[16] and in the peripheral leukocytes of patients with acute varicella.[11] Chromosomal breaks have been described in the leukocytes of one child whose mother had gestational varicella.[95] An increased risk for leukemia in the offspring of women with gestational varicella has been noted by several investigators, but the numbers are too small to allow definite conclusions as to whether this is a true association.[101]

Several case reports published over the past 40 years have described the occurrence of congenital malformations in the offspring of women who develop chickenpox during pregnancy.[3,5,15,19,21,26,32,42,44,45,48,55,64,72,84,85,88,97,106,114,120,127,134,149–151,165] With the exception of one infant with congenital skin ulcers following maternal varicella

Table 4. *Clinicopathologic Abnormalities in Newborns Following Maternal Gestational Varicella*

TIME OF VIRUS TRANSMISSION	ABNORMALITY
Weeks 8 to 20 of pregnancy	Cicatricial skin lesions, denuded skin, limb hypoplasia, muscular atrophy, rudimentary digits, clubfoot, intrauterine growth retardation, microcephaly, cerebellar and cortical atrophy, seizures, brain calcifications, Horner's syndrome, psychomotor retardation, sensory deficits, microphthalmia, optic atrophy, cataract, chorioretinitis, nystagmus, recurrent aspiration pneumonia, dysphagia, anal sphincter dysfunction, herpes zoster
Last 3 weeks of pregnancy	Fever, vesicular rash, hemorrhagic rash, cyanosis, respiratory distress, pneumonia, widespread necrotic lesions of the viscera (in fatal cases)

at 28 weeks of gestation,[10] these infections usually occurred between the 8th and 20th weeks of pregnancy. Abnormalities are primarily cutaneous, musculoskeletal, neurologic, and ocular as summarized in Table 4.

Unilateral cicatricial lesions involving a hypoplastic limb are the most common skin abnormalities. These cutaneous scars may involve the opposite extremity as well, and they sometimes extend to the trunk. Limb hypoplasia is usually unilateral and most commonly involves the leg. The arm, mandible, or hemithorax can be affected, however. Rudimentary digits are commonly noted in hypoplastic extremities. Detailed clinical and histopathologic studies of some patients suggest that limb abnormalities following *in utero* VZV infection are probably due to a neuropathy resulting from damage to dorsal ganglia and anterior columns of the spinal cord.[120,134]

Neurologic abnormalities are common and include microcephaly, cortical and cerebellar atrophy, seizures, psychomotor retardation, and focal brain calcifications. Autonomic dysfunction, manifested by loss of bowel and urinary sphincter control, dysphagia, intestinal obstruction, and Horner's syndrome, is seen in some patients. Unilateral or bilateral ocular abnormalities are common (see Table 4) and the eye may be the only organ affected in fetal VZV infection.

A small number of infants born with congenital malformations following maternal herpes zoster during pregnancy have been described in the literature.[20,46,81,158] Reported defects include microcephaly, microphthalmia, cataracts, and talipes equinovarus. These rare cases may represent chance occurrences rather than true associations. Paryani and Arvin[106] prospectively followed 14 pregnancies complicated by herpes zoster and could find no clinical or immunologic evidence of intrauterine VZV infection.

VZV has been isolated from the vesicular fluid of one newborn

with encephalitis and herpes zoster following maternal varicella in early pregnancy.[15] All other attempts at viral isolation from body fluids or organs of affected infants have failed.

Management of these infants consists of supportive medical therapy and surgery for correctable defects. Isolation of these patients is not necessary unless they have herpes zoster. Many die in infancy.

Neonatal Infection

One of four newborns will become infected when maternal varicella occurs during the last 3 weeks of pregnancy.[98] The most important determinant of the severity of neonatal disease is the time of onset of maternal varicella relative to delivery. When maternal infection occurs within 4 days before and 2 days after delivery, varicella lesions in neonates will usually appear at 5 to 10 days of age. The illness may be mild with only a few cutaneous lesions, or may become severe with fever, hemorrhagic rash, and generalized visceral involvement (see Table 4). The mortality rate is about 30 per cent and death usually is due to severe pulmonary disease. When maternal varicella occurs 5 to 21 days before delivery, lesions in newborns typically appear in the first 4 days of life and the prognosis is good with no associated mortality. The mild course is probably due to the production and transplacental passage of maternal antibodies, which modify the course of the illness in newborns.

The diagnosis can be confirmed by viral isolation, antigen detection, or serology, as already discussed. Newborns with varicella should be kept in strict isolation if they require hospitalization. Vidarabine or acyclovir can be used for infants with severe disease, although neither drug is licensed for this purpose. Administration of VZIG is of no benefit once clinical disease has developed.

Prevention

Proper management of persons exposed to VZV is critical because varicella is a highly communicable infection that can affect pregnant women and their offspring adversely. Exposed susceptible persons can be protected by passive immunization with pooled immune serum globulin (ISG), zoster immune globulin (ZIG), or varicella-zoster immune globulin (VZIG). ZIG is obtained from herpes zoster patients during their convalescent stage, whereas VZIG is prepared from plasma of normal blood donors who are found to have high IgG antibody titers to VZV. ZIG and VZIG are comparable products but the latter is available in greater supplies. ISG contains less than a tenth of the anti-VZV antibodies found in ZIG or VZIG and should not be used unless the two other preparations are unavailable. ZIG and VZIG can prevent or modify clinical varicella in susceptible persons if given shortly after exposure.

A live, attenuated varicella vaccine is available but awaits licensing in the United States. Extensive trials have shown it to be effective and safe.[57,160] There are no guidelines for its use yet, but adults susceptible to varicella probably will benefit from the vaccine.

The first step in managing pregnant women exposed to VZV is to ascertain whether they are susceptible to the virus. A carefully elicited history of a previous varicella infection is considered sufficient evidence of immunity. Clinical reinfections can occur but are rare. The second step is to decide if exposure is likely to result in infection. Situations involving prolonged contact with varicella patients, as within a family, place susceptible adults at a very high risk (90 per cent) of contracting the infection.

Pregnant women exposed to varicella who have negative or uncertain prior histories of this infection should be tested for VZV susceptibility if sensitive assays are available and the results can be obtained rapidly. About 80 to 95 per cent of these women will be found to be immune to varicella as indicated by a positive CF, IAHA, FAMA, or ELISA test result.[27,96] CF antibody assays are not very sensitive and negative test results may not necessarily imply susceptibility to VZV. The significance of low anti-VZV antibody titers detected by sensitive tests is unclear because some of these persons have developed clinical varicella following exposure. An intradermal skin test that uses heat-inactivated VZV antigen has been shown to correlate very well with the results of sensitive serologic assays, but it is not available except for research purposes.[90]

Once it is determined that a pregnant woman with significant exposure to varicella is susceptible, or if the laboratory test results cannot be obtained in a short period, ZIG or VZIG should be administered for the purpose of preventing or modifying the infection in the mother to avoid complications. It is not known whether passive immunization of mothers will prevent fetal VZV infection.[27] ZIG and VZIG are most effective when given as soon as possible after exposure, but not later than 96 hours.

The risk of congenital malformations following first trimester maternal varicella is estimated at 5 per cent.[106] Borzyskowski and colleagues[19] reported a set of female identical twins sharing a single placenta whose mother developed varicella at 10 weeks' gestation. The first twin was normal while the second had congenital defects consistent with intrauterine VZV infection. Prenatal diagnosis by detection of VZV-specific IgM in fetal blood has been successful in one fetus evaluated at about 32 weeks of gestation, approximately 12 weeks after his mother developed chickenpox.[44]

Infants born to mothers who develop varicella within 5 days before and 2 days after delivery should receive 125 units of VZIG as soon as possible. ZIG and VZIG do not reduce the clinical attack rate in treated newborns, but these newborns develop milder infections when compared with untreated neonates.[27,68] Because severe varicella may develop in newborns despite ZIG or VZIG administration,[12] some investigators have advocated the use of acyclovir prophylaxis in these infants as well.[63] Although a few cases of severe varicella in neonates exposed to mothers who develop the infection more than 2 days after delivery have been described,[117] routine ZIG or VZIG administration is not currently recommended because this group of in-

fants is not generally considered to be at increased risk of complications from this disease.[27]

Women with varicella at the time of delivery should be isolated from their newborns until all vesicles have crusted. Neonates with varicella lesions should be isolated from other infants but not from their mothers.

EPSTEIN-BARR VIRUS

Maternal Infection

Infection with Epstein-Barr virus (EBV) is very common during childhood. Most adults, especially those of lower socioeconomic status, have serologic evidence of prior EBV infection. Seroepidemiologic studies of pregnant women have shown that 95 per cent or more have evidence of previous exposure to the virus.[51,74,76,92]

Primary EBV infection in pregnancy is uncommon. Seroconversion occurred in only 3 of more than 12,000 pregnant women evaluated in prospective studies.[140] The frequency estimate is higher when one considers only seronegative susceptible pregnant women. Fleisher and Bologonese[51] documented seroconversion during gestation in three (7 per cent) of 46 seronegative mothers. Icart and colleagues[76] noted that 6 (0.2 per cent) of 2684 seropositive women tested in the first trimester of pregnancy had a serologic profile indicative of a primary EBV infection. Other workers[74,92] noted no seroconversion among approximately 140 pregnant women followed prospectively. Reactivation of latent EBV infection as suggested by changes in anti-EBV antibody profiles and oropharyngeal viral shedding appears to be more common during pregnancy than at other times.[41,50,140]

More than half of all primary EBV infections are subclinical. Adults are more likely than children to have symptomatic disease. Infectious mononucleosis is the most common clinical manifestation of EBV infection and usually is self-limited. Complications are infrequent but may include airway obstruction, meningoencephalitis, Guillain-Barré syndrome, splenic rupture, and, rarely, death. EBV also has been associated with Burkitt's lymphoma, nasopharyngeal carcinoma, lymphoproliferative disorders in renal or bone marrow transplant recipients, and X-linked lymphoproliferative syndrome. Associations between EBV and several other conditions have been described in the literature, but these are not firmly established at present.[7]

Laboratory diagnosis of EBV infections is based most commonly on serology. The detection of heterophil antibodies in patients with infectious mononucleosis is considered diagnostic of a primary EBV infection, although there is a small frequency of false-positive reactions. EBV-specific serology can be used in those with a negative heterophil antibody test. Antibodies against several EBV antigens are produced at different times during the course of an infection. Typi-

cally, antibodies to EBV viral capsid antigen (VCA) and early antigen (EA) appear during the acute phase of the infection while those against EBV nuclear antigen (EBNA) develop weeks to months later.[148] Primary infections can be diagnosed by detecting IgM antibodies to VCA, but the result of this serologic test may be falsely positive if the serum contains rheumatoid factor. If no IgM antibodies are detected, then the presence of IgG antibodies to VCA and EA and none against EBNA is suggestive of either a primary or postacute infection. IgG antibodies to VCA and EA are usually at their peak very early in the illness in 80 to 90 per cent of patients. Fourfold or greater increases in antibody titers between acute and convalescent sera therefore are documented only occasionally. EBV isolation using lymphocyte transformation assays, genome detection using DNA hybridization, and detection of EBNA in tissues by anticomplement indirect immunofluorescence staining are useful for diagnosis, but these methods are mostly employed in research studies and are not widely available.

Treatment of infectious mononucleosis is supportive. Corticosteroids usually are used in patients with airway obstruction, severe thrombocytopenia, or hemolytic anemia. Acyclovir inhibits oropharyngeal shedding of EBV, but this effect is reversible on discontinuation of the drug. Acyclovir does not seem to hasten the resolution of any one symptom, but the total time for recovery from the illness appears to be shorter in treated compared with untreated patients.[6]

Maternofetal Transmission

Although not well established at the present time, it appears that transplacental transmission of EBV does occur, but very rarely. Fleisher and Bologonese[51,52] prospectively studied six women with serologically proven infectious mononucleosis or primary asymptomatic EBV infection in early pregnancy but could find no serologic or virologic evidence of EBV infection in their offspring. Using spontaneous transformation of cord blood lymphocytes to estimate the frequency of congenital EBV infection, Chang and co-workers[30,31] found only 1 of over 2696 specimens to be positive. This infant was clinically normal, and EBV infection could not be documented by serology. Visintine and colleagues[154] studied a group of 150 infants including premature and full-term neonates, infants with congenital malformations, and others suspected of having a TORCH infection. One otherwise normal premature infant had oropharyngeal EBV shedding at 16 days of age. Serology was not done until 2 months of age and was positive, but his lymphocytes showed no spontaneous transformation. This patient's lymphocytes became positive for EBV at 4 months of age, but he remained developmentally normal until his last followup at 2 years of age. Joncas and co-workers[77] studied lymphocytes of 137 newborns but found no evidence of EBV transmission to the fetus. Two neonates with multiple congenital malformations associated with virologic and serologic evidence of EBV infection have been described in the literature, and they provide good evidence for the occurrence of *in utero* EBV infections.[59,78]

Ornoy and co-workers[105] reported the placental findings in five women who developed infectious mononucleosis during the first 2 months of pregnancy. All pregnancies were terminated by 3 to 5 months of gestation and the major pathologic changes included a necrotizing deciduitis, villitis, and chorioamnionitis. One fetus had congenital malformations, and two of three fetuses examined had histologic evidence of myocarditis. This study provides additional indirect evidence that EBV can be transmitted transplacentally and produce a fetal infection.

The possibility of EBV acquisition by neonates during passage through the birth canal should now be considered. Sixbey and colleagues[130] recently demonstrated cervical EBV shedding in 5 (18 per cent) of 28 women using lymphocyte transformation assays and DNA hybridization studies. These intriguing data need further confirmation because earlier work by other investigators failed to demonstrate cervical shedding of this virus.[31,154] Pregnant women at various stages of pregnancy and at delivery should be studied to define the frequency of EBV cervical shedding and to assess the potential risks for newborns.

Fetal Infection

It is difficult to determine with certainty which effects EBV infections have on the outcome of pregnancy. Primary EBV infections are rare in pregnancy,[51,92] and newborns may not acquire the virus altogether or may be subclinically infected.[14,51,52] However, a few published case reports describe the association of gestational infectious mononucleosis with a variety of congenital defects.[24,93,105] Reactivation of EBV infection during pregnancy does not appear to affect its outcome adversely. The outcome for infants born to EBV-seropositive women with respect to the incidence of low birth weight or congenital malformations was similar for 295 neonates whose mothers had reactivation of their EBV infections during gestation and 341 other newborns whose mothers did not.[41,50,119] Icart and colleagues,[76] however, studied 719 seropositive pregnant women and noted that those who were anti-EA positive were significantly more likely to have an abnormal pregnancy outcome compared to women negative for this antibody. These investigators did not perform any virologic or serologic studies on the offspring of these women, and one cannot be certain what role, if any, EBV infections had with the reported adverse pregnancy outcome.

Various congenital defects have been described in the few reported infants with documented congenital EBV infection or whose mothers had infectious mononucleosis during pregnancy.[24,59,93,99,105,157] No specific pattern can be recognized. Reported abnormalities include among others low birth weight, micrognathia, low-set ears, myositis, congenital heart disease, biliary atresia, central nervous system malformations, cataract, microphthalmia, skin laxity, metaphyseal lucencies, and hip dysplasia. The patient described by Joncas and coworkers[78] had a concomitant congenital CMV infection, and the de-

scribed abnormalities were consistent with cytomegalic inclusion disease. The contribution of EBV to the observed malformations could not be ascertained.

The diagnosis of congenital EBV infection can be established serologically or by attempting viral identification using lymphocyte transformation assays as previously discussed. Management of these infants is supportive, and no specific therapy is currently available.

Prevention

There are no specific preventive measures. Susceptible pregnant women should avoid contact with infectious mononucleosis patients to reduce their risk of infection, although intimate contact usually is needed for transmission to occur. Women who develop primary EBV infection during pregnancy are not candidates for therapeutic abortions but should be informed of the rare reported instances of congenital malformations associated with this infection. Pregnant women with EBV reactivation probably are not at increased risk for an adverse pregnancy outcome. There are no available vaccines for susceptible persons.

CONCLUSIONS

Maternal herpesvirus infections during gestation are potentially hazardous to the normal development of the embryo or fetus. The magnitude and nature of these risks depend largely on the etiologic agent involved, the timing of the insult during gestation, and whether the infection is primary. In this review, we used gestational herpesvirus infections to illustrate the variability in pregnancy outcome for different agents, and for the same virus when infection occurs at different times during the course of pregnancy. Proper management of both mother and fetus hinges on establishing an accurate etiologic diagnosis. The possibilities for prenatal diagnosis of fetal infection presently are limited, but recent new approaches appear promising. In spite of their limitations, strategies aimed at preventing maternal or fetal infection are the best approach to the problem of herpesvirus infections in pregnancy at this time.

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Perinatal Echovirus and Group B Coxsackievirus Infections

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HISTORY

During the epidemics of poliomyelitis that occurred in North America prior to the introduction of poliomyelitis vaccines, it was observed that pregnant women suffered paralytic disease that was more common and more severe than in nonpregnant women.[1–8] Perinatal transmission of poliomyelitis was observed when maternal infection occurred late in pregnancy, resulting in paralytic infection of newborn infants that was frequently fatal.[9]

With the decline of paralytic poliomyelitis in the developed world, the coxsackieviruses and the echoviruses assumed more importance as causes of serious newborn infections. Outbreaks of group B coxsackievirus disease were first reported in nurseries in South Africa and Rhodesia.[10–13] Since then many cases of neonatal disease due to both the group B coxsackieviruses and the echoviruses have been reported to occur sporadically as well as during nursery outbreaks.[14]

ENTEROVIRUS NOMENCLATURE

The *picornaviridae* are a sizable family of small (27 nm), single-strand RNA viruses that include both human enteroviruses and rhinoviruses. The 67 recognized enterovirus serotypes are distinguished from one another by neutralization with type-specific antisera.[15] These 67 serotypes were traditionally grouped into four classes (polioviruses, group A coxsackieviruses, group B coxsackieviruses, and echoviruses), but newly discovered serotypes are now designated *enteroviruses* (e.g., enterovirus 70).

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EPIDEMIOLOGY AND CLINICAL DISEASE

Enterovirus infections are extremely common, the risk varying with age, standard of living, season, and climate. Infection occurs in young children at a higher rate than among older children and adults, and there is an inverse relationship between prevalence of enterovirus infection and socioeconomic status. In northern latitudes, enterovirus infections are most prevalent during the summer and fall but may occur at any time of the year. This seasonal periodicity is less pronounced in more tropical climates. Some serotypes are isolated frequently (e.g., group B coxsackievirus types 2-5 and echovirus types 4, 6, 9, and 11), whereas other serotypes are rarely reported.[16] Group A coxsackievirus disease is underrecognized clinically and underreported because many of the Group A coxsackieviruses grow poorly or not at all in routine cell culture.

Most enterovirus infections are either asymptomatic or cause simple febrile illnesses with or without signs of upper respiratory infection or rash.[17] Some clinical syndromes are characteristically associated with enterovirus infection, including aseptic meningitis, pleurodynia, and the hand–foot–mouth syndrome. Host factors, including age, sex, pregnancy, vigorous exercise, and immune status, are important determinants of the severity of infection.

STUDIES IN EXPERIMENTAL ANIMALS

Several investigators have demonstrated that pregnancy enhances enterovirus infection in laboratory mice.[18–23] Pregnant mice experimentally infected with several different human enteroviruses have a shorter incubation period,[18, 19] develop higher titers of virus in the blood and various organs,[22, 23] and remain viremic longer[21, 22] than do nonpregnant mice. Susceptibility increases with advancing gestation[18, 22] and rapidly reverts to that of nonpregnant animals within days of delivery.[18] The causes of the diminished resistance of the late gestational animal to enterovirus infection are largely unknown, but may be mediated by hormonal influences. Farber and Glasgow have demonstrated that resistance of nonpregnant female mice to encephalomyocarditis virus infection could be reduced by administration of corticosterone or estrogen but was not altered by exogenous progesterone.[24]

Group B coxsackievirus infection of the pregnant mouse also results in infection of the fetus prior to delivery or in infection of the newborn mouse intrapartum.[25–27] The effect on the fetus or newborn mouse depends on the gestational stage in which the pregnant dam is infected. Early infection of the pregnant mouse produces a high rate of fetal loss due to resorption and abortion.[20, 21, 26, 27] If the pregnant mouse is infected after 12 days of gestation, virus reaches the fetus *in utero* in a small minority of pregnancies, producing stillbirth and postnatal death among pups delivered at term.[20, 21, 25, 27] However,

the placenta appears to be an effective but not impenetrable barrier to fetal infection, perhaps because of macrophage activity within the placenta.[21, 27, 28]

NONPOLIO ENTEROVIRUS INFECTIONS IN PREGNANT WOMEN

The risk of enterovirus infection during pregnancy depends on a complex series of factors, including the time of year, the risk of exposure to young children, the prevalence of pathogenic enteroviruses in the community, and the presence or absence of prior immunity to the prevalent enterovirus serotype(s). Several studies have found surprisingly high rates of enterovirus infection during pregnancy. The NIH Collaborative Perinatal Project noted serologic evidence of infection with group B coxsackieviruses in 9 per cent of 198 unselected women studied over the course of their pregnancies.[29] Cherry and his colleagues found a seroconversion rate to common enterovirus serotypes of 25 per cent among 55 women followed prospectively over the final 2 to 6 weeks of pregnancy during peak enterovirus season.[30] Another study conducted during an echovirus 11 outbreak in Boston found a point prevalence of 3.4 per cent among women admitted in labor,[31] a figure that would have undoubtedly been considerably higher had the period of observation extended to the several weeks prior to parturition. In the latter two studies, most infected pregnant women were either asymptomatic or had only mild, nonspecific illnesses, and none gave birth to infants with severe enterovirus infections. Thus, prospective surveillance data indicate that enterovirus infection late in pregnancy is a very common event during periods of high prevalence of community infection, but most infections do not produce significant maternal or neonatal morbidity.

In contrast, 59 to 65 per cent of women who give birth to infants with reported echovirus or group B coxsackievirus infection have documented symptomatic illnesses during the perinatal period.[32–34] Maternal echovirus infection late in gestation may produce a brief but sometimes severe illness characterized by fever and lower abdominal pain. An incorrect diagnosis of abruptio placenta[35–37] or appendicitis[38, 39] in some of these cases has led to emergency cesarean delivery. The pathophysiology of these symptoms is not known, but pathologic findings in one case strongly supported a diagnosis of mesenteric adenitis.[39] Echoviruses have been isolated from throat swabs,[37] feces,[35, 37, 40] and vaginal[39] or cervical secretions[41] of some of these women. Mothers of infants with reported group B coxsackievirus infections have had febrile illnesses with upper respiratory symptoms, pleurodynia,[34, 42–46] myocarditis,[47] and aseptic meningitis.[48, 49] Maternal infection has been confirmed by isolation of virus from the oropharynx,[48] feces,[34, 44, 48, 49] and CSF,[48, 49] and by a rise in neutralizing antibody titer.[42, 44, 50]

Spontaneous Abortion, Stillbirth, and Teratogenicity

Gestational poliomyelitis was reported to end with spontaneous abortion in 13 to 24 per cent of pregnancies,[5, 8, 51–54] but there are no data to link maternal infection with echoviruses or group B coxsackieviruses to an increased risk of early fetal wastage. Data from two echovirus 9 epidemics indicated no increase in the rate of spontaneous abortion in pregnant women with serologic evidence of infection during pregnancy.[55, 56] Stillbirth late in pregnancy has been reported following maternal echovirus and maternal group B coxsackievirus infections. Two stillborn infants have been reported to have been delivered near term to women who each had febrile illnesses due to echovirus 11, 5 to 10 days earlier. Virus was isolated from the amniotic fluid in one case,[57] but culture of multiple fetal organs in the second case was negative.[58] Coxsackievirus B antigens have been reported in the myocardial tissue of four stillborn fetuses near term.[59, 60]

Studies of maternal infection with wild[9, 52, 53, 61] and attenuated[62] polioviruses, and echovirus 9,[55, 56, 63] have consistently shown no increased risk or consistent pattern of fetal malformation. A series of studies in which seroconversion to selected enterovirus serotypes was tested in a large number of pregnancies found a slight but significant risk of congenital heart defects and urogenital anomalies among infants born to women who had seroconverted to the group B coxsackieviruses.[64–66] No seasonal influences on the specific malformations were observed, however. Furthermore, this study was subject to certain methodologic errors, and thus the findings must be considered highly tentative.

ENTEROVIRUS INFECTIONS OF NEWBORN INFANTS

Incidence

The true incidence of neonatal enterovirus infections is unknown. With the exception of poliomyelitis, enterovirus infections are not nationally reportable, and there are no population-based, prospective studies of the incidence of neonatal enterovirus infection. One study based on laboratory records suggested a minimal rate of group B coxsackievirus infections of 50 per 100,000 among infants born in Nassau County, New York, from 1970 to 1979.[34] For comparison, the estimated incidence of perinatally acquired herpes simplex infection is 1 per 7500 live births, or 13 per 100,000.[67]

The CDC Enteroviral Surveillance Program, which is largely based on passive reporting from public health laboratories, provides some data regarding the occurrence of neonatal disease for each of the enterovirus classes relative to one another. Over the 4-year period from 1972 to 1975, 51 per cent of reported 338 infants under 2 months of age had echovirus infections, compared with 45 and 4 per cent respectively for the group B coxsackieviruses and the group A coxsackieviruses.[68] Seventy-four per cent of these cases were classified as

"severe" based on a diagnosis of CNS disease, systemic illness, hepatitis, myocarditis, or death. Lake and his colleagues also found a higher prevalence of echovirus disease at four University of Colorado affiliated hospitals over a 6-year period. Eighteen (67 per cent) of their twenty-seven neonatal cases had echovirus infections, compared with seven (26 per cent) group B coxsackievirus infections and two (7 per cent) group A coxsackievirus infections.[69]

Mechanisms of Transmission

Neonatal enterovirus infection is most often acquired directly from the mother during parturition, or from maternal or nonmaternal sources in the postnatal period. The age-specific incidence for newborn echovirus and group B coxsackievirus infections peaks between 3 and 7 days of life, strongly suggesting that infection is acquired in the immediate perinatal period.[32, 33] The actual route of transmission from mother to infant is not known. Contact with virus-containing maternal secretions during vaginal delivery is one plausible explanation. Not only might enteroviruses from the gastrointestinal tract contaminate the maternal perineum, but echovirus 11 has been recovered from the vaginal[39] and cervical[41] secretions of pregnant women who have delivered infants who subsequently developed infection. However, because 40 to 50 per cent of infants who have subsequently developed echovirus disease[32] and 10 to 15 per cent of infants with coxsackie B virus infections[33] were born via cesarean delivery, passage through the maternal birth canal is not a prerequisite for vertical transmission of enteroviruses. It is likely that contact with other maternal sources of virus such as blood[70] or upper respiratory tract secretions are routes of vertical enterovirus transmission.

Regardless of the route, rate of transmission to the infant from mothers with documented enterovirus infection in the perinatal period is relatively high. Cherry and his colleagues witnessed mother-to-infant transmission in 4 of 14 (29 per cent) mothers with documented echovirus 17, coxsackie B2, or coxsackie B5 infections.[30] Similarly, during an echovirus 11 outbreak, our group found that four of seven women who were excreting virus during labor in either their oropharyngeal secretions or feces transmitted this virus to their newborn infants within 3 days of birth.[31]

Enteroviruses also are transmitted *in utero* prior to delivery as well as during parturition and the postpartum period. Echovirus 11 has been recovered from cord blood[39] and coxsackie B1 virus has been recovered from amniotic fluid,[34] in both cases from infants with signs of infection at birth. Furthermore, 6 (11 per cent) of 54 reported infants with echovirus infection developed signs of infection within 48 hours of birth,[32] and 22 per cent of reported infants with fatal group B coxsackievirus infections were ill on the first day of life.[34]

Postnatal transmission to the newborn infant from both maternal and nonmaternal sources also occurs regularly.[40, 71–73] Echoviruses[40, 73–77] and group B coxsackieviruses[14, 78] have been recovered from hospital personnel having close contact with infected infants, and se-

rologic methods have been used to trace the spread of neonatal echovirus infection by medical and nursing staff.[77] The mechanism of postnatal transmission by hospital personnel is not known, but it presumably involves direct contact between the caretaker and the infant. Gavage feeding of sequential patients by nursing personnel was implicated as a mode of spread of echovirus 11 in one nursery outbreak,[78] and spread of coxsackie B4 virus infection via routine mouth care was demonstrated in another chronic care facility for bedridden pediatric patients.[79]

Clinical Manifestations

The manifestations of neonatal enterovirus disease range from inapparent infection to overwhelming systemic illness and death. Numerous clinical features are recorded in the literature, including exanthem, enanthem, pneumonia, gastroenteritis, necrotizing enterocolitis, hepatitis, pancreatitis, myocarditis, meningoencephalitis and paralysis, generalized hemorrhage, complete peripheral vascular collapse, and sudden infant death. The varied clinical manifestations have been thoroughly reviewed by Cherry.[1-1] This summary is limited to the most characteristic and most serious clinical syndromes associated with neonatal echovirus and group B coxsackievirus infections.

Serious neonatal echovirus infections nearly always become apparent within the first 7 days of life, although rare cases are recorded beyond this age.[32, 36] Echovirus infection is more common in male infants, and approximately half of reported infected infants are born prematurely,[32] in part because of preterm cesarean delivery following acute maternal echovirus illness.[37–39]

The most common clinical expression of neonatal echovirus infection is CNS disease, either meningitis or meningoencephalitis. Neonatal echovirus CNS infection is sometimes accompanied by pneumonia[80, 81] or myocarditis.[82] The deaths that follow CNS infection seem to occur in those infants with simultaneous myocarditis or pneumonia. CNS echovirus infection is usually self-limited, but survivors may be subject to adverse neurologic sequelae.[83, 84]

A second, more severe, syndrome results from systemic infection in which the liver is the prime target organ. Although this syndrome has been referred to as a "sepsis-like" illness, the clinical manifestations can be fully attributed to the massive hepatic necrosis caused by echovirus infection. The presenting signs and symptoms resemble those of bacterial sepsis—lethargy, poor feeding, and apnea, but then the disease progresses rapidly to jaundice and hypocoagulability.[37, 85] Serum transaminase levels may reach 5000 IU or higher, and both the prothrombin time and partial thromboplastin time are extremely prolonged. The management of the severe hepatitis syndrome is often complicated by extensive spontaneous bleeding from multiple sites, including the skin, gastrointestinal tract, renal medullae, lungs, and ventricles of the brain.[85–87] Despite heroic therapy with blood, platelets, and fresh frozen plasma, more than 80 per cent of these infants die.[32] Autopsy findings include extensive necrosis and

inflammatory infiltrates of the hepatic parenchyma, and frequently of the adrenals.[85, 87] With the exception of interstitial and intraluminal hemorrhage, other organs such as the brain, heart, and kidneys show little evidence of virus-induced inflammation or necrosis. Unfortunately, there is little information on the long-term prognosis of the few infants who survive.

As with echovirus disease, most serious group B coxsackievirus infections in neonates have occurred at less than 10 days of age. There is a 1.8 to 1 predominance of infection in male infants,[33, 34] and about one third of reported cases have been premature. Data from nursery outbreaks of group B coxsackievirus infections indicate that many infants are asymptomatically infected or have only mild, nonspecific febrile illnesses.[14, 88] More severe infections occur in the form of disease of the CNS, the heart, or both. Lethargy, coma, seizures, and focal neurologic signs are suggestive of meningoencephalitis, while infants with myocarditis present with feeding difficulties, listlessness, respiratory distress, cyanosis, fever, jaundice, and diarrhea.[89] Additional evidence of myocardial infection includes tachycardia, arrhythmias, cardiomegaly, and ECG abnormalities, especially low voltage. Many infected infants have a biphasic presentation in which nonspecific symptoms precede clinical evidence of myocarditis by several days.[89] In addition to meningoencephalitis and myocarditis, some infants have clinical or postmortem evidence of hepatitis, pancreatitis, or pneumonia. Rare cases of severe hepatitis have been reported due to coxsackie B1[34] and coxsackie B3.[90] A review by Kibrick in 1961 found a mortality rate of 53 per cent among 45 reported infants with myocarditis.[89] There are no recent data to indicate whether modern neonatal intensive care has improved the prognosis for infants with group B coxsackievirus myocarditis.

Factors Associated with Outcome

The severity and outcome of infection of perinatally acquired enterovirus infection are influenced by several factors, including the virus strain, the mode of transmission, and the presence of passively acquired, serotype-specific maternal antibody. In recent years, echovirus 11 has proved inherently more virulent for newborn infants than other echovirus serotypes. A recent review found that echovirus 11 accounted for 70 per cent of all cases of reported serious neonatal disease.[32] Several coxsackie B serotypes appear highly virulent for the newborn infant, especially serotypes B2, B3, B4, and B5.[14] Coxsackie B1 virus has been reported infrequently to cause severe illness, whereas, to my knowledge, there are no reports of neonatal disease due to coxsackie B6 virus.

The clinical literature suggests that the mechanism and timing of enterovirus transmission to the newborn infant are important determinants of the severity of infection. Infants who acquire infection vertically from their mothers *in utero* or in the immediate peripartum period are much more likely to develop severe disease than are infants

who become infected later as a result of postnatal transmission from maternal or nonmaternal sources.[32]

It is now fairly well established that the presence or absence of serotype-specific, passively acquired transplacental antibody will modify enterovirus infection in the newborn infant. It has long been known that maternal antibody will interfere with live, attenuated poliovirus vaccine infection in newborns.[91] More recently, data from Boston and from Cambridge, England, have shown that maternal antibody protects against neonatal disease due to echovirus 11 but does not necessarily prevent infection.[31, 37, 92, 93] Thus, the timing of maternal infection in relation to delivery is an important determinant of outcome of infection for the newborn infant. Maternal infections occurring more than 5 to 7 days prior to delivery are likely to induce maternal IgG antibody that will cross the placenta prior to birth, protecting the newborn against disease but not necessarily infection.[31] Infants born to mothers who become infected closer to delivery are at higher risk of severe disease, in part because of absence of passively acquired antibody.

OUTBREAKS OF DISEASE IN NEWBORN NURSERIES

There are several reports of newborn nursery outbreaks of nonpolio enterovirus infection from many countries, including the United States, Great Britain, Australia, South Africa, Germany, and Japan.[10–13, 40, 72–74, 76–77, 88, 92–107] Most outbreaks have been due to echovirus 11 or to group B coxsackievirus serotypes 1 to 5, and most have coincided with seasonal peaks of enterovirus disease in the community. Both regular nurseries for term infants and special care nurseries have experienced outbreaks, sometimes in the same institution.[74, 75] Attack rates of clinical illness have varied from 22 to 54 per cent; in some reports, a small number of infants have been identified who were asymptomatically infected.

The source of infection has been traced to infants vertically infected from their mothers[40, 76, 77, 96] or to infected personnel. In most outbreaks the source of infection is not known, however. Once infection is introduced, spread occurs via direct contact between nursery personnel and the newborn infants. Both echoviruses[40, 73–77] and group B coxsackieviruses[13, 93] have been recovered from nurses and physicians caring for infected infants. Although the mode of spread is not known, it is likely that contamination of the hands of personnel is an important factor.[78, 79] A recent investigation of an echovirus 11 outbreak in Winnipeg indicated that mouth care and gavage feeding were highly associated with spread of infection from personnel to neonates.[78]

Interestingly, infants infected during outbreaks of echovirus infection have had mostly brief and self-limited illnesses with fever, rash, apnea, diarrhea, or aseptic meningitis. Nonspecific clinical man-

ifestations also have predominated among newborns infected during group B coxsackievirus outbreaks, although aseptic meningitis was the dominant clinical illness in three reported outbreaks caused by coxsackie B2[107] and B5[93, 102, 104] viruses, and myocarditis has occurred during outbreaks due to coxsackie B2,[107] B3,[11, 13] B4,[12] and B5.[102, 104]

Efforts to control the spread of enterovirus infection have included the administration of immune serum globulin (ISG) to uninfected infants and closure of the nursery to new admissions.[101, 108, 109] However, the use of ISG during an echovirus 11 outbreak in Winnipeg suggested little benefit,[78] and complete closure of the nursery may be an unnecessarily drastic measure. In the absence of better outbreak control data, cohorting of infants with identified infection and rigorous attention to hand washing by all nursery personnel are likely to be sufficient control measures.[11]

SUMMARY

Enteroviral infections late in pregnancy are common, especially during periods of high prevalence of community infection. Most of these infections, however, are not associated with significant maternal or neonatal disease. Conversely, as many as 65 per cent of women who give birth to infants with proven enteroviral infection have symptomatic disease during the perinatal period. Maternal echovirus or coxsackievirus B infections are not associated with an increased risk of spontaneous abortions, but stillbirths late in pregnancy have been described. Although a slightly increased risk for congenital heart defects and urogenital anomalies has been reported for the offspring of women who seroconverted to the group B coxsackievirus during pregnancy, these data are highly tentative. Transmission of enteroviruses from mother to infant is relatively common (30–50 per cent) and may occur through contact with maternal secretions during vaginal delivery, blood, or upper respiratory tract secretions. Intrauterine transmission has been documented, but its frequency is unknown. Postnatal transmission from maternal or nonmaternal sources also occurs regularly. Neonatal disease may range from inapparent infection to overwhelming systemic illness and death. Common clinical syndromes associated with neonatal enteroviral infections are meningoencephalitis, pneumonia, myocarditis, and hepatitis. The severity and outcome of perinatally acquired enteroviral infection is influenced by several factors, including the virus strain involved, mode of transmission, and presence of passively acquired serotype-specific maternal antibody. Newborn nursery outbreaks of nonpolio enteroviral infections usually coincide with seasonal peaks of enteroviral disease in the community. These outbreaks have been due mostly to echovirus 11 or group B coxsackievirus serotypes 1 to 5 and are associated with attack rates of up to 50 per cent.

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Maternal Rubella and the Congenital Rubella Syndrome

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The concept of an infectious etiology for congenital malformations is not new,[18] but convincing evidence in its support was lacking until 1941, when the Australian ophthalmologist N. McAlister Gregg[17] described the association of maternal rubella infection during pregnancy and the occurrence of congenital defects in their offspring. In his description of 78 patients with congenital cataracts, Gregg noted that most of these infants were small for age, had feeding difficulties, and that many suffered from congenital heart abnormalities. A history of maternal German measles during pregnancy was elicited in 68 (87 per cent) instances. Our knowledge of the spectrum of fetal and neonatal disease following gestational rubella has increased considerably since publication of Gregg's report. We also recognize now that not all untoward effects of rubella are apparent at birth and that this infection has other nonteratogenic but devastating effects on fetal development, such as miscarriages, abortions, and stillbirths.

With the availability and widespread use of safe and effective rubella vaccines, the goal of eradicating this infection has become theoretically achievable. The number of infants born with the congenital rubella syndrome has declined to record low levels in the United States. However, a significant proportion of women of childbearing age continue to be susceptible to rubella. It is therefore essential that health care providers be vigilant in identifying women at risk and offer them protection through vaccination.

MATERNAL INFECTION

Rubella is a mild infection that occurs worldwide. Its importance derives from its teratogenic effects on the fetus when rubella afflicts

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pregnant women. The epidemiology of this infection in the United States has changed dramatically since licensure of the rubella vaccine in 1969. In the prevaccine era, rubella was most common among children 5 to 9 years of age and the level of immunity for the population was 85 per cent by 15 to 19 years of age and almost 100 per cent by 35 to 40 years.[20] Epidemics occurred at 6- to 9-year intervals and major pandemics every 10 to 30 years.[1] The last pandemic of the mid-1960s resulted in an estimated 11,000 miscarriages, abortions, and stillbirths, and about 20,000 newborns with the congenital rubella syndrome.[2] Widespread rubella vaccination has resulted in dramatic declines in incidence rates for all age groups. Data from the Centers for Disease Control (CDC) for 1986 show only 551 reported rubella cases in the United States, a 99 per cent decline from 1969.[6] Of these cases, about 58 per cent were patients 15 years of age or older. Seroepidemiologic surveys indicate that currently 12 to 24 per cent of postpubertal individuals are susceptible to rubella infection, and this allows for the continued transmission of rubella virus among females in the reproductive age group.[2] Rubella outbreaks have been reported from Chicago, the San Francisco Bay area, and New York City over the past 10 years in the United States.[4]

The infection is subclinical in a large proportion of patients. Symptomatic disease is typically mild and occurs 14 to 21 days following exposure of susceptible people to the virus. A mild prodrome consisting of malaise, low-grade fever, headache, and conjunctivitis may precede the rash by 1 to 5 days. The rash is macular, begins on the face and behind the ears, spreads downward over 1 to 2 days, and usually disappears over 3 days. Postauricular, suboccipital, and posterior cervical lymphadenopathy are typically present. Transient arthralgias may occur in up to one third of infected adult women, but arthritis is uncommon. Other complications are rare and include thrombocytopenic purpura, neuritis, and encephalitis.

The diagnosis of rubella on clinical grounds alone is unreliable because a similar illness may be produced by enteroviral infections, mild measles, or human parvovirus B19 disease. Serologic confirmation therefore is essential, especially in pregnant women for whom a diagnosis of rubella has very serious implications. Shirley and coworkers[30] investigated 627 patients clinically suspected of having rubella but could confirm this diagnosis serologically in only 229 (37 per cent) instances. Their study included 135 pregnant women, of whom only 41 (30 per cent) were found to actually have this infection. Many serologic tests are currently available, and these include hemagglutination inhibition (HI), enzyme-linked immunosorbent assay (ELISA), immunofluorescence, radioimmunoassay, hemolysis in gel, and passive agglutination tests.[19] Serum specimens obtained as soon as possible after the appearance of the rash and again 2 weeks later can establish the diagnosis if a fourfold or greater rise in antibody titer can be documented. The detection of rubella-specific IgM in a single serum sample obtained within 28 days after appearance of the rash is also diagnostic. Cross-reactions between rubella and human parvo-

virus infections in specific IgM tests have been described, thereby necessitating caution in interpreting low or equivocal levels of rubella-specific IgM antibodies.

Therapy of postnatal rubella is symptomatic. These patients shed the virus from the nasopharynx for 1 week before and 1 week after onset of the rash. The virus is also present in blood and urine during the week preceding the rash but disappears thereafter. Transmission is by droplet spread, and isolation of these patients is recommended during the period of nasopharyngeal shedding.

MATERNOFETAL TRANSMISSION

Maternal viremia is a prerequisite for placental and fetal rubella infection. Most cases occur following primary disease. Rubella reinfections are uncommon but can occur in women with previous naturally acquired rubella or vaccine recipients. The risk of fetal damage from reinfections appears to be very small even when they occur early in pregnancy.[12, 14–16, 21, 24]

The frequency of intrauterine transmission of rubella virus and the outcome of fetal infection is dependent on the gestational timing of maternal rubella. It should be remembered, however, that estimates of gestational age are imprecise because we do not usually know when fertilization takes place exactly, when fetal infection actually occurs, if the incubation period in the fetus is similar to that of postnatal rubella infection, and how long it takes to infect a significant number of embryonic cells.[31]

Fetal infection may occur following maternal rubella at any stage of pregnancy.[10, 23] Miller and co-workers[23] prospectively evaluated 1016 women with confirmed rubella during pregnancy. Only 407 (40 per cent) continued their pregnancy to term. The rate of congenital infection following maternal rubella was 81 per cent during the first 12 weeks of pregnancy, 54 per cent at 13 to 16 weeks, 36 per cent at 17 to 22 weeks, 30 per cent at 23 to 30 weeks, and then rose to 60 per cent at 31 to 36 weeks and 100 per cent for those occurring in the last month of pregnancy. Cardiac defects and deafness occurred in all infants infected during the first 10 weeks of gestation, and deafness alone was noted in a third of those infected at 13 to 16 weeks. No rubella defects were noted in those infected after the 16th week. More recently, Munro and colleagues[25] reported their findings on 106 infants with confirmed congenital rubella syndrome in whom the maternal infection was proved serologically, thereby allowing a fairly accurate assessment of gestational age at the time of infection. Deafness was documented in 58 per cent of these patients and was the only abnormality in 40 per cent of cases. Infants with congenital cardiac, ocular, or central nervous system (CNS) defects almost always had deafness. They also noted that the risk of deafness was very small when infection occurred after the 16th week of gestation.

FETAL INFECTION

As a result of the rubella vaccination programs in the United States, the number of infants born with the congenital rubella syndrome (CRS) has declined to record low levels. In 1979, 57 cases of CRS were reported. This figure had dropped to two cases in each of the years 1984 and 1985.[6] However, 12 cases of CRS were reported during 1986, 8 of which followed a rubella outbreak in New York City in 1985.[4, 6] Only two cases of CRS have been reported to the CDC during the first 9 months of 1987. These figures underestimate the true frequency of CRS, since mild cases may not be recognized until later in life and other outcomes of fetal infection such as miscarriages, abortions, or stillbirths are not measured by current surveillance methods.

The mechanisms by which rubella virus causes fetal damage are poorly understood. Infected cells have reduced mitotic activity as a result of chromosomal breaks[7] or the production of a protein that inhibits mitosis.[27] Focal cytolysis secondary to infection of cells with the rubella virus can be found in many organs, but inflammation is not a prominent feature of congenital rubella. Much of the pathology in this infection appears to be secondary to vascular damage. Damaged endothelial cells can act as a source of virus-infected emboli and also lead to small blood vessel thrombosis.[35] The delayed manifestations of congenital rubella may be due to viral persistence with resultant ongoing damage or to immune mechanisms, such as autoimmunity, circulating rubella-specific immune complexes, or to defective cytotoxic effector cell function.[9, 36]

Over half of all newborns with congenital rubella are normal at birth, but the majority later develop one or more signs and symptoms of disease. The most common abnormalities in CRS listed in order of decreasing frequency are hearing loss, mental retardation, cardiac malformations, and ocular defects.[31] Sensorineural hearing loss is the only serious abnormality that may present as the sole manifestation of CRS.[8] Cardiovascular anomalies are rare when maternal rubella occurs after the first trimester.[26] Other defects that are encountered in CRS are summarized in Table 1.

If one includes mental retardation and infection of neurosensory organs such as the eyes and ears, then signs and symptoms of CNS involvement are found in over 80 per cent of CRS patients.[37] Rubella virus can be isolated from the cerebrospinal fluid of a third of all patients, and the virus may persist for up to a year of age in severely affected infants. Vascular abnormalities, a prominent pathologic feature in congenital rubella, sometimes contribute to the neuropathology by causing ischemic necrosis of adjacent tissue.

Postnatal growth of patients with CRS appears to be related to the time at which infection occurs during gestation.[34] When exposure occurs early in gestation, as evidenced by cataract formation, patients typically have retarded growth in their height and body weight when

Table 1. *Clinicopathologic Abnormalities in Congenital Rubella*

ABNORMALITY	COMMENT
General	
Intrauterine growth retardation	Common
Prematurity	Infrequent
Abortion	Infrequent
Stillbirth	Infrequent
Cardiovascular system	
Patent ductus arteriosus	Common; may occur with pulmonary artery stenosis
Pulmonary artery stenosis	Common; due to intimal proliferation
Coarctation of the aorta	Infrequent
Myocarditis	Infrequent
Ventricular septal defect	Rare
Atrial septal defect	Rare
Eye	
Cataract	Common; unilateral or bilateral; usually present at birth
Retinopathy	Common; "salt-and-pepper" appearance; frequently unilateral; visual acuity unaffected
Cloudy cornea	Rare; spontaneous resolution
Glaucoma	Rare; may be bilateral; usually present at birth but may be delayed in appearance; leads to blindness if not recognized
Microphthalmia	Common in patients with unilateral cataract
Subretinal neovascularization	Develops in some patients with retinopathy during late childhood or adolescence; causes macular scarring with loss of vision
Hearing loss	Very common; usually bilateral; most commonly sensorineural but may be central in origin; rare when maternal rubella occurs after fourth month of gestation; may be present at birth or develop later in childhood; sometimes progressive
Central nervous system	
Meningoencephalitis	Common; transient
Microcephaly	Uncommon; may be associated with normal intelligence
Intracranial calcifications	Rare
Electroencephalographic abnormalities	Common; usually disappear by one year of age
Mental retardation	Common
Behavioral disorders	Common
Autism	Infrequent
Chronic progressive panencephalitis	Rare; males affected; manifests in second decade of life
Hypotonia	Common
Speech defects	Uncommon in absence of hearing loss
Skin	
"Blueberry muffin" spots	Infrequent; represents dermal erythropoiesis
Chronic rubelliform rash	Usually generalized and lasts several weeks; appears in infancy
Dermatoglyphic abnormalities	Common
Interstitial pneumonia	Infrequent; generalized; probably immunologically mediated

(*table continues next page*)

Table 1. *(Continued)*

ABNORMALITY	COMMENT
Liver	
Hepatosplenomegaly	Common; transient
Jaundice	Infrequent; usually appears in first day of life
Hepatitis	Rare; may not be associated with jaundice
Blood	
Thrombocytopenic purpura	Common; transient; no response to steroid therapy
Anemia	Infrequent; transient
Hemolytic anemia	Rare; transient
Altered blood group expression	Rare
Immune system	
Hypogammaglobulinemia	Uncommon; transient
Lymphadenopathy	Uncommon; transient
Thymic hypoplasia	Uncommon; fatal
Bone	
Radiographic lucencies	Common; transient; most common in distal femur and proximal tibia
Large anterior fontanelle	Uncommon
Micrognathia	Infrequent
Endocrine glands	
Diabetes mellitus	Common; usually becomes apparent in second or third decade
Thyroid disease	Hypothyroidism, hyperthyroidism, and thyroiditis may occur but infrequently
Growth hormone deficiency	Rare
Genitourinary system	
Cryptorchidism	Uncommon
Polycystic kidney	Rare

compared with other CRS children and healthy age-matched controls. Patients with CRS infected at an apparently later stage of pregnancy exhibit slow growth rates during the preschool years, but they catch up with the general population thereafter. The head circumference is smaller than that of age-matched controls for all patients with CRS, but this abnormality is most pronounced in those with cataracts.

The appearance of delayed manifestations of CRS that were not present in early life underscores the importance of careful follow-up of these patients. Diabetes mellitus occurs in about 20 per cent of patients by 35 years of age, and thyroid abnormalities may be found in about 5 per cent. Ten per cent of CRS patients develop additional forms of eye damage, such as glaucoma, keratoconus, and spontaneous lens resorption.[29] Progressive rubella panencephalitis is a rare but an ultimately fatal delayed manifestation of CRS.

The diagnosis of CRS usually is suspected on the basis of the maternal history or the clinical findings. A definitive diagnosis can be reached by recovering the virus from pharyngeal washings or, less commonly, from urine or cerebrospinal fluid. The virus persists in the nasopharynx for 6 to 12 months. Viral isolation is seldom resorted to

Table 2. *Summary of Centers for Disease Control Criteria for the Classification of Congenital Rubella Syndrome Cases*

CRS Confirmed Presence of defects and at least one of the following: A. Isolation of rubella virus B. Detection of rubella-specific IgM antibodies C. Rubella-specific HI titer in the infant persisting beyond the period expected from that of passively transferred maternal antibodies
CRS Compatible Insufficient laboratory data for confirmation of diagnosis and any two complications from A or one from A and one from B: A. Cataracts or congenital glaucoma, congenital heart disease, hearing loss, pigmentary retinopathy B. Purpura, splenomegaly, jaundice, radiolucent bone disease, meningoencephalitis, microcephaly, mental retardation
CRS Possible Presence of some compatible clinical findings but insufficient criteria for either the confirmed or compatible categories
Congenital Rubella Infection Only No defects are present, but laboratory evidence of infection is found.
Stillbirths Stillbirths believed to be a consequence of maternal rubella infection
Not CRS At least one of the following inconsistent laboratory findings in an immunocompetent child: A. Absence of rubella-specific HI titer in a child younger than 2 years of age B. Absence of rubella-specific HI titer in the mother C. Decline in rubella-specific HI titer in an infant in a manner consistent with what is expected from passively transferred maternal antibodies (a twofold dilution drop per month)

in practice because of its difficulty and expense. Rubella-specific IgM is usually present in congenitally infected infants and may persist for 6 to 12 months and can be used to make a definitive diagnosis. Persistence of rubella-specific IgG antibodies at 6 to 12 months of age, especially in high titers, provides presumptive evidence of congenital or early postnatal infection. Table 2 summarizes the criteria used by the Centers for Disease Control for the classification of CRS cases.[4]

There is no specific therapy for CRS. Susceptible pregnant women should avoid contact with these patients during the first year of life. Careful followup for the detection of delayed manifestations, surgical correction of heart defects and cataracts, and special schooling may be needed in many patients.

PREVENTION

The rubella vaccine is recommended for all persons who are 12 months of age or older unless they are immune. A clinical diagnosis of rubella is unreliable and hence cannot be used as proof for immunity. Persons are considered immune if they have serologic evi-

dence of immunity or had previously been vaccinated on or after their first birthday.[3] The currently available RA 27/3 live, attenuated vaccine induces long-lasting immunity in about 95 per cent of recipients.

If a previously unimmunized pregnant woman is exposed to rubella, it is essential to test her for antibody to rubella because up to 20 per cent of women of childbearing age are susceptible. If the woman is immune, then the risk of reinfection is very small, and fetal risks from these reinfections also are small. Susceptible women, on the other hand, should be informed of the risks of fetal damage should they develop the infection. The use of immune serum globulin following exposure does not prevent maternal infection or viremia, nor does it protect against fetal infection.

Women who contract rubella during the first 5 months of pregnancy should consider a therapeutic abortion. Infections occurring after this time do not produce congenital defects. Because not every fetus becomes infected following maternal rubella, some investigators have attempted to determine fetal status prenatally. The virus has been isolated from the amniotic fluid in a few cases, but the sensitivity of this method is not known. This is also limited by the need to wait until about 16 weeks of gestation before amniocentesis can be performed and by the time required to grow the virus, thereby delaying pregnancy termination if infection is present. Daffos and co-workers[11] obtained fetal blood from 18 pregnancies at 20 to 26 weeks of gestation and performed rubella-specific IgM assays. Because this antibody does not cross the placenta, the detection of rubella-specific IgM is considered diagnostic of fetal infection as long as there is no contamination of fetal blood specimens by maternal blood. These investigators detected rubella-specific IgM in 12 fetuses. Only one of the six fetuses without detectable antibody was found to be infected at birth. The limitations of this method are that the fetus does not make IgM until the fifth month of gestation, and the amount produced may be small initially and below the limits of detection. Enders and Jonatha[13] recently reported their experience with the prenatal diagnosis of fetal rubella infection through the detection of rubella-specific IgM antibodies in fetal blood obtained between weeks 21 and 23 of pregnancy. These studies were helpful in the management of 28 of 31 pregnancies. Two patients had undetectable rubella-specific IgM antibodies but were born with CRS. In two other cases, rubella-specific IgM antibodies were detected. One pregnancy was terminated and rubella virus was isolated from placental and fetal tissues. The second pregnancy was continued, and an apparently healthy but infected neonate was delivered. Terry and colleagues[32] detected rubella antigen and ribonucleic acid sequences in a chorionic villus biopsy specimen obtained at 11 weeks of gestation from a woman with a clinical diagnosis of rubella in early pregnancy. This led to termination of pregnancy by the 13th week, and rubella infection was confirmed in both the aborted fetus and placenta. This technique is very specialized and cannot be performed by routine diagnostic laboratories, but it appears to be promising.

Susceptible pregnant women who do not acquire rubella usually have been immunized in the immediate postpartum period. This practice may have to be revised in view of some recent reports indicating that as many as 8 per cent of women receiving the RA 27/3 vaccine in the postpartum period develop acute arthritis and that some go on to develop a chronic arthropathy, neurologic abnormalities such as the carpal tunnel syndrome or multiple paresthesias, and a chronic rubella viremia.[33] These women also shed the vaccine virus in breast milk, leading to infection of some breastfed infants.[22] Some of these infants may develop a chronic rubella viremia.[33] These data are of a preliminary nature at the present time and are considered insufficient to alter the currently recommended practice of postpartum rubella immunization of all susceptible women.[28]

The rubella vaccine should not be administered during pregnancy because of theoretic risks to the developing fetus. Recent data indicate that none of 522 infants born to 635 pregnant women inadvertently immunized with the RA 27/3 vaccine since 1979 in the United States had defects compatible with CRS.[5] The vaccine virus, however, does cross the placenta and produces a subclinical infection in 1 to 2 per cent of infants born to previously susceptible vaccinees. Women who are vaccinated within 3 months before or after conception are not candidates for therapeutic abortions because of the minimal risk involved.

SUMMARY

The major goal of rubella immunization is the prevention of the congenital rubella syndrome. As many as 20 per cent of women in the reproductive age group in the United States continue to be susceptible to rubella despite the immunization programs currently in place. Intensified efforts are therefore needed to identify persons at risk for infection and to vaccinate them. Women who develop a rubella-like illness during pregnancy should have the diagnosis confirmed serologically because a diagnosis based on clinical criteria alone is unreliable and because of the serious implications of gestational rubella infection. The rubella virus can infect the fetus at any stage of pregnancy, but defects are rarely noted when this occurs after the 16th week of gestation. The most common abnormalities in the congenital rubella syndrome are hearing loss, mental retardation, cardiac malformations, and eye defects. Diabetes mellitus, thyroid disease, glaucoma, and other delayed manifestations of congenital rubella syndrome are common, thereby necessitating long-term followup of these patients. The detection of rubella-specific IgM antibodies in fetal blood is helpful in establishing the diagnosis prenatally and can aid in the management of pregnancies complicated by this infection. Susceptible women identified through screening during pregnancy should be immunized in the immediate postpartum or postabortion period. Although the live, attenuated rubella vaccine is contraindi-

cated during pregnancy, pregnant women who are inadvertently immunized are not candidates for pregnancy termination because no defects consistent with congenital rubella have been reported to date in the offspring of other similarly vaccinated women.

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Uncommon Virus Infections of the Mother, Fetus, and Newborn: Influenza, Mumps and Measles

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INFLUENZA

Maternal influenza is common, but the extent of fetal involvement is unknown. The literature is replete with studies that have sought to document fetal outcomes of maternal infection. The search for a rubella-like pattern of pathogenesis has been unrewarding. An array of conclusions, usually resulting from suboptimal study circumstances, has resulted in perplexing uncertainty regarding the role of maternal infection in abortion, stillbirth, prematurity, and particularly in congenital malformations. The question of transplacental passage of virus, for example, has been convincingly demonstrated in isolated reports,[24,28,35,47] but there is no reasonable estimate of its frequency during epidemics. In the same context, observations that suggest a cause-and-effect relationship between influenza and congenital anomalies do not predictably reappear in subsequent epidemics. Even in the years between epidemics, influenza is a relatively common infection. The toll it takes on elderly and chronically debilitated persons is well known but its effects on the fetus remain enigmatic.

Influenza Virus

Three major antigens have been identified for the virus, Types A and C. Type A causes most epidemics and severe illnesses; Type B is less frequently involved. Type C is apparently of little clinical importance. Subclassification by surface antigen involves four hemagglutinins (H0, H1, H2, and H3), and two neuraminidase subtypes (N1 and N2). Individual strains are identified by a string of identifiers. For example, A/Bangkok/1/79 (H3N2) designates a specific viral strain.

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The A refers to the major antigen type. Bangkok indicates geographic location of the laboratory in which the strain was first isolated. The laboratory's sample number and the year the strain was isolated are represented by 1/79. Hemagglutinin and neuraminidase subtypes are indicated by H3N2.

Influenza virus was first isolated in 1933. In that year Type A was identified; in 1940 Type B was identified.[9,21,40] It then seemed possible that relationships between typed organisms of maternal infection and fetal abnormalities might be delineated. Since that time, however, major changes in antigenic constituency have been noted repeatedly, "antigenic shifts." Minor changes have also occurred and they are called "antigenic drifts." Shifting and drifting through the years have precipitated problems in the preparation of appropriate vaccines and also have complicated the identification of cause and effect relationships between maternal infection and fetal outcome.

CLINICAL COURSE

Influenza is a respiratory infection characterized by cough, sore throat, fever, generalized aches, and acute debilitation. The incubation period ranges from 1 to 4 days. Illness persists for approximately 5 days followed by a period of fatigue and weakness. Recovery is the rule.

Spread of disease usually occurs by droplets between individual persons and by this modality community epidemics are probably propagated. Pandemics such as those of 1918 and 1957 and 1958 seem to arise spontaneously and synchronously throughout the world in areas that are geographically remote from each other. Since the 1950s, as a result of mass travel, the world has become a community, at least in regard to communicability of disease. High mortality during the pandemic of 1918 has been attributed to pneumonia, mostly influenzal but also caused by superimposed bacterial infection[45] by *Staphylococcus aureus*, *Streptococcus pneumoniae*, and gram-negative rods such as *Klebsiella*. The near-pandemic of 1957 and 1958 was characterized by illness of less severity and by a considerably diminished incidence of complications.

Maternal Infection

Influenza is asymptomatic in a significant segment of an infected population. Three informative studies have related symptomatology to serologic response. Wilson and Stein[46] reported that 60 per cent of asymptomatic pregnant women had serologic evidence of recent infection. On the other hand, there was no serologic evidence of infection in 35 per cent of the women who reported symptoms. Hardy et al.[15] reported the same phenomenon. Twenty-four per cent of symptomatic women were serologically negative; 39 per cent of asymptomatic women were serologically positive. Walker and McKee[44] identified 398 women whose serology was positive for influenza during

an epidemic. Fifty per cent were asymptomatic. The data from these three reports explain in part the diverse conclusions of many studies in which maternal symptomatology during epidemics was the sole indicator of infection.

A definitive diagnosis of influenza can be established by virus isolation from the respiratory tract, demonstration of viral antigens in nasopharyngeal epithelial cells, or by means of serology. Appropriate specimens for virus isolation include nasopharyngeal or throat swabs, nasal washings, or sputum. Most positive culture results are usually obtained within 3 to 7 days. Detection of influenza virus antigens in nasopharyngeal cells using fluorescein-conjugated virus-specific antibodies can provide a rapid diagnosis in some patients. The diagnosis also can be made serologically by demonstrating a fourfold or greater rise in virus-specific IgG antibody titers or by detection of virus-specific IgM antibodies. The most commonly employed serologic tests are the complement fixation, hemagglutination inhibition, or ELISA tests.

Infection becomes more virulent during epidemics. In 1918 mortality rates among pregnant women varied from 30 to 50 per cent. Later epidemics were not associated with mortality of such magnitude. There is no evidence that pregnancy predisposes to infection or to an enhanced severity of illness.

Hardy et al.[15] demonstrated an increased rate of stillbirths among women who had symptoms and serologic evidence of infection compared to those who were either asymptomatic or serologically negative or both. In contrast, the second study of Coffey and Jessop in 1959[6] did not indicate an increased incidence of stillbirth or prematurity among infected mothers, save for those whose infants were congenitally defective.

Fatal infection has been reported, but rarely during the past few decades. In 1971, Yawn et al.[47] described a woman who was infected during the third trimester. Virus was isolated from lungs, hilar nodes, heart, spleen, liver, kidney, brain, spinal cord, amniotic fluid, and fetal myocardium. The mother died of pulmonary edema. In 1980 another report[33] described third trimester infection in a 23-year-old woman. At autopsy, virus was isolated from her tracheal mucosa, lungs, and pulmonary blood; at death, *Streptococcus pneumoniae* was also cultured from the blood. Antibody to the virus was not detectable.

Transplacental Passage and Fetal Infection

Influenza virus has not been isolated from blood but nevertheless transplacental passage has been documented by Yawn et al.[47] and by McGregor et al.[24] The former investigators described a fetal infection during the last trimester of pregnancy in which influenza A2/Hong Kong/8/68 was isolated at autopsy from a variety of maternal extrapulmonary tissues, from the amniotic fluid, and from the fetal heart (see maternal infection). The latter report concerned a 24-year-old multigravida who was infected at 36 weeks' gestation. During the acute illness, virus was recovered from nasal washings and from un-

contaminated amniotic fluid. At delivery of a normal infant 3 weeks after the mother's recovery from influenza, the virus could not be isolated from the infant's nasal washings, from the placenta nor amniotic fluid. Maternal serology indicated a hemagglutination inhibition titer of 1:32 for influenza A/Bangkok (H3N2) and a complement fixation titer of >1:52. In cord blood, hemagglutination inhibition titer was 1:8 and complement fixation was 1:64 for influenza A. IgM and IgA isotypes were elevated in cord blood, confirming the presence of antenatal fetal infection. Transplacental passage of the virus was associated with uterine tenderness, simulating bacterial chorioamnionitis. Fetal tachycardia also was noted during the mother's acute illness. Although virus was cultured from amniotic fluid 3 weeks before delivery, the infant was virus free at birth. In 1980 Ramphal et al.[33] described a different experience with a fatal case of maternal pneumonia due to influenza. Transplacental passage of virus was not demonstrated, although virus was isolated at autopsy from maternal tracheal mucosa, lungs, and pulmonary blood. Fetal viral cultures from amnion, placenta, lung, tracheal mucosa, pleural fluid, and blood were all negative.

It is thus clear that transplacental passage of influenza virus does occur, implying antecedent viremia though virus has never been cultured from blood. If viremia occurs, it must be of such short duration as to preclude detection.

Congenital Malformations

Unlike maternal rubella and cytomegalovirus infections, there is no discernible pattern of fetal malformations attributable to influenza. Several considerations seem to militate against the formulation of clear conclusions from the numerous published studies. Major antigenic shifts, identified over the past several decades, may impair comparison of one epidemic to another. Furthermore most studies have relied solely upon signs and symptoms for diagnosis of infection, but the reported inconsistencies between symptomatology and serologic responses makes such diagnoses highly questionable. Patterns of the congenital defects associated with maternal infection have been inscrutable. They have also varied geographically. In Ireland the preponderant anomaly was neural tube defect. In the United States cardiac malformations were predominant, and neural tube defects were not observed. In Finland, central nervous system defects were common, but they did not include anencephaly. It is conceivable that during epidemics, infection merely enhances preexisting vulnerability to congenital malformations. In those circumstances a universal pattern unique to influenza virus would not be expected. If there were such a distinct pattern, it should have been discernible during the many epidemics that have been studied in years past.

Manson et al. studied an influenza epidemic in England between 1950 and 1952.[22] Infection was identified clinically by a physician; only those women confined to bed for at least 24 hours were included in the analysis. One hundred and sixty-six pregnancies were identi-

fied; in ninety-nine of them infection occurred between the 13th and 28th weeks. Fetal outcomes of infected gravida were not significantly different from controls, but it is noteworthy that these were second trimester infections. In 1955, Coffey and Jessop[5] reported over 12,000 total births in Dublin during an epidemic. Mothers completed a questionnaire as soon as feasible after delivery. Among the mothers who had given birth to abnormal infants, 18.4 per cent reported symptoms compatible with influenza infection. Among mothers who were normal, only 3.6 per cent indicated symptoms of infection. Anencephaly was the most common abnormality. Four years later,[5] these same investigators prospectively collected information from women who attended antenatal clinics at a time when influenza virus was known to be widespread in the community. Serologic tests were not performed. The incidence of congenital malformations among women who reported symptoms was 2.4 times greater than asymptomatic controls. Defects of the central nervous system were the most numerous. There were 10 cases of anencephaly among the 24 defective neonates born of infected mothers. Spina bifida, hydrocephaly, meningomyelocele, and Down's syndrome compose most of the remainder. It is particularly interesting that the distribution of defects among infected and uninfected mothers was similar, although the overall incidence of infection was higher in mothers of defective infants. The risk of defect was greater in the first trimester than in the second; greater in the second trimester than in the third. The similar distribution of abnormalities among the infected and control groups suggests that infection could have enhanced an existing predisposition to anencephaly in the studied population. In contrast to these findings, Doll et al.[7] did not detect a fetal hazard among infected mothers, even during the first trimester.

Hardy et al.[15] included serologic and clinical observations in their study. The incidence of fetal malformation was higher among mothers whose serologic responses indicated gestational influenza. Vulnerability was greater during the first trimester, but not a single neural tube defect was identified.

Nosocomial Infection in the Neonate

Neonatal nosocomial infection is not rare even though passive transfer of maternal antibody probably prevents infection during the neonatal period and for a few months thereafter.[32] Bauer et al.[3] described two infants whose illnesses were characterized by fever, irritability, and nasal discharge; they both recovered a few days after the onset of illness. The virus isolated from both infants was influenza A/Hong Kong/68. Meibalane et al.[26] reported more severe illnesses characterized by apnea, lethargy and poor feeding. Two of eight infected infants in this nursery outbreak had cough and nasal congestion. The chest films of three infants revealed a pattern consistent with interstitial pneumonia. Joshi et al.[18] reported fatal influenza A2 pneumonia in a neonate.

A report based on data from the Collaborative Perinatal Study[19]

described outcomes of 52 mothers whose samples, taken during varying trimesters, demonstrated seroconversion to Influenza A (Asian). Study infants did not differ significantly from matched controls respect to neonatal status, neurologic status at 1 and 4 years of age, and IQ at 4 years.

SUMMARY

The literature is appropriately preoccupied with attempts to clarify the relationship between maternal influenza and fetal malformation.[14,20,48] A distinct pattern has not emerged, frequent epidemics and numerous studies notwithstanding. Transplacental passage of virus is documented but rare. Impediments to consistent conclusions include: antigenic shifts from one epidemic to another, reliance on clinical observations to identify affected mothers in the face of discrepancies between symptomatology and serology, a dearth of virologic and serologic data, variations in ethnicity and geography of study populations, and a paucity of prospective studies in large populations. At present one can only surmise that if influenzal disease is in fact culpable, it increases the incidence of congenital malformations that otherwise occur with less frequency.

MUMPS

Mumps Virus

Mumps is a paramyxovirus with an "S" antigen associated with the envelope, and a "V" antigen in the core. The envelope (S) antigen is cross-reactive with other paramyxoviruses; the core (V antigen) is more specific. Both are CF antigens but hemagglutinin is also demonstrable in the envelope. The virus is easily grown in several media including African green monkey kidney cells, embryonated hen's eggs, and human cells.

CLINICAL COURSE AND EPIDEMIOLOGY

Mumps is a contagious disease that most prominently involves swelling of the parotids. It is usually febrile and generalized, as indicated by such symptoms as malaise and aching. Other organs are affected with varying frequency. Orchitis occurs in 20 per cent of infected males after puberty; ovary involvement is considerably less frequent. Thyroiditis and mastitis occur in postpubertal females. The other salivary glands also may be involved, but not in the absence of parotid swelling. Pancreatitis is infrequent; nephritis, myocarditis, and arthritis are rare. Mumps meningitis has been reported in 5 to 25 per cent of affected patients. Virus isolation and pleocytosis in spinal

fluid frequently are noted in asymptomatic patients. On a rare occasion, cranial nerve involvement has been reported; deafness is the most often cited residual.

The incubation period varies widely; in the extreme it may be 7 to 23 days, but in most instances incubation is 14 to 18 days. During the first 3 days of symptoms, virus is isolated from throat, urine, and saliva. If the course is complicated by meningitis, the virus also is cultured from spinal fluid. Mumps virus is shed from urine for several days (up to 2 weeks) following disappearance from other sites. It has also been cultured from blood, breast milk, and testes. Dissemination generally occurs by droplets and fomites.

Estimates of the incidence of mumps during pregnancy vary from 0.8 to 10 cases per 10,000 population. The disease is no more severe in pregnant women than in nonpregnant patients of the same age. Approximately 30 per cent of these infections are asymptomatic; inapparent disease has been reported in as many as 60 per cent of documented infections.[31]

Spontaneous abortion occurs more frequently in infected patients than in controls. Abortions usually occur within 2 weeks of disease onset. In 1973, a prospective study by Siegel[39] reported abortion in 27 per cent of infected gravidas during the first trimester, compared to 13 per cent of controls. The incidence of prematurity was unaffected by mumps.

Congenital Malformations

The risk of fetal malformation in infected mothers is unknown. In the study by Siegel,[39] congenital malformations were as common in infected as in uninfected gravidas. Associations between gestational mumps and fetal malformation have been reported in anectodal or uncontrolled studies. Abnormalities have been reported in the skin, gastrointestinal tract, eye, and genitourinary tract. The retrospective study of Manson et al.[23] reviewed the course of 501 infected gravida. They found no significant increase in the incidence of congenital malformation.

In animals, gestational mumps has been associated with myocardial necrosis, cataracts, and stenosis of the aqueduct of Sylvius. There is no evidence of such associations in humans, except for the myocardial necrosis. This observation often is cited in support of the relationship of maternal mumps to fetal endocardial fibroelastosis.

Endocardial Fibroelastosis

The lesion of endocardial fibroelastosis is characterized by a thickened, yellowish-white subendocardium. The surface of the endocardium retains a smooth glistening appearance. It most often is associated with intracardiac structural abnormalities that obstruct blood flow, particularly on the left side of the heart. The subendocardial thickening that has been described in mumps is more generalized; it is unrelated to structural anomalies that cause abnormal intracardiac flow. Endocardial fibroelastosis also has been described

as a residuum of fetal myocarditis due to coxsackievirus. The incidence has diminished sharply and unaccountably during the past 15 to 20 years.

The link with maternal mumps is controversial. It was first reported by Noren et al.[30] in 1963, when a strong association between the cardiac lesion and a reactive mumps skin test was identified. Within 3 years, 3 studies had made similar observations.[37,41,43] St. Geme et al.[41] noted delayed cutaneous hypersensitivity in 13 of 14 infants in whom endocardial fibroelastosis was identified. Neutralizing antibodies were demonstrated in only two of them. In no instance was virus cultured either from the oropharynx or at autopsy from the heart. The authors suggested that the lesion was a residuum of fetal mumps myocarditis. They explained the contradictory absence of humoral antibodies and positive skin hypersensitivity as manifestations of a "split" immunologic reactivity that is characterized by a cellular response (T cells) in the absence of a humoral response (B cell response). The authors postulated that this may be an ontogenetic recapitulation of phylogenetic development. Immune reactions of lower animals are restricted to cellular response. St. Geme et al.[42] later demonstrated the "split" phenomenon in rhesus monkey fetuses. Furthermore there is suggestive evidence of its existence in humans.[1] Data from the mumps epidemic on St. Lawrence Island (an isolated island in the Bering Sea off the coast of Alaska) revealed that 10 of 12 children born of infected mothers had reactive skin tests in the absence of demonstrable neutralizing antibodies. In the mothers themselves, both skin sensitivity and humoral antibodies were demonstrated.

There is evidence for disagreement with the postulated relationship between maternal mumps and endocardial fibroelastosis. Some investigators have not been able to demonstrate a difference in the incidence of positive skin test results among infected patients and controls.[12,13,29] Furthermore, the skin test is thought to be nonspecific, probably cross-reacting with similar antigens in parainfluenza virus. The concept of "split" immune responses is not an acceptable explanation to some of these investigators. They believe that the absence of humoral antibodies to mumps documents the absence of previous infection. There is no available evidence to resolve this controversy. The incidence of endocardial fibroelastosis began to diminish before the advent of mumps vaccine. Prior to this decline in incidence, the risk of endocardial fibroelastosis was estimated at 2 per cent of infants born of infected mothers.[27,41] Since introduction of the vaccine, gestational mumps and endocardial fibroelastosis have become absolute rarities.

Postnatal Infection

Clinical mumps is rare in the neonate. Jones et al.[17] described 3 mother–infant pairs in whom maternal mumps is said to have occurred. One mother delivered a male infant while she was febrile and symptomatic 6 days after the onset of mumps. The infant had bilateral

parotid swelling and his subsequent course was uncomplicated. Mumps skin test result was positive at 42 days of age and at 12 years of age the child was normal. Another febrile mother delivered a male infant 4 days after the onset of her infection, while parotids were enlarged. At 7 days of age this infant was febrile, he coughed, fed poorly, and ultimately required mechanical ventilatory support for approximately 10 days. Both mother and infant had significant elevations of antibody titers to S and V antigens. A third infected mother delivered a male infant who had neither clinical nor serologic evidence of infection. Neonatal mumps is rare.

SUMMARY

Gestational mumps is a benign infection that has not been shown to cause fetal malformations.[14,49] It has been associated with an increased rate of abortion during the first trimester, but not with an increase in premature births. When it occurs late in pregnancy, mumps rarely affects the neonate. The association of endocardial fibroelastosis with maternal mumps is persistently controversial.

MEASLES

Measles Virus

Measles, in the paramyxovirus family, differs from other members of that group by virtue of an absence of neuraminidase. It is readily cultured in human embryonic kidney and rhesus monkey kidney cells; a cytopathic effect is identifiable in 5 to 10 days. Virus isolates are identified further in antiserum by hemadsorption inhibition or plaque reduction tests. Measles virus does not cross-react with other members of the paramyxovirus group. Hemagglutination inhibition is the preferred technique for demonstration of antibodies. Complement fixation is less sensitive for the identification of past infections.

EPIDEMIOLOGY

Spread from one person to another is by droplets; portals of entry are presumably the oropharnyx, nose, and conjunctivae.

In the United States, before the introduction of measles vaccine in 1963, epidemics recurred every 2 to 3 years. They are now unusual, occurring sporadically in limited circumscribed areas such as the epidemics in colleges that have occurred in recent years.[10] In the prevaccine era approximately 500,000 cases of measles were reported annually; among them 400 to 500 deaths were associated with measles.[25] In the 1980s the annual incidence of measles has varied be-

tween 1500 and 3000 reported cases. The percent decline in age-specific incidence rates has been greatest in children below 10 years, and consequently the age distribution of infection is radically altered. Before availability of a vaccine, measles was predominantly a disease of the 2- to 6-year-old child. Between 1976 and 1980, however, 46 per cent of the reported cases occurred in children over 10 years of age, compared to 9.9 per cent in the years before immunization.[10] In spite of this gross shift in age distribution, preschool children are still preponderantly affected. Approximately 25 per cent of all reported cases occur at 4 years of age or less.

Communicability and pattern of disease vary according to several population characteristics, such as age, socioeconomic status, geography, and previous experience with measles. Attack rates are higher in less favored socioeconomic populations. In urban industrial communities, the disease was concentrated in the 2- to 6-year-age group and it was relatively mild, whereas in a rural setting the affected age group was older. As a result, larger segments of a rural population reached adulthood uninfected than was the case in urban communities. It follows that infection during pregnancy would occur more frequently in rural and isolated communities.[49]

In underdeveloped countries the pattern of disease is most sinister. In Africa, for example, measles is characteristically a disease of children below 2 years of age, with an awesome, high mortality rate. Complications, particularly bronchopneumonia, are far more frequent in such populations, and this has been attributed largely to a steady state of protein deficiency.

The pattern of disease in virgin populations (which usually reside in isolated locations) is also different. Frequent reference is made to the classic epidemic in the Faroe Islands in 1846, in which a 100 per cent attack rate was recorded.[2] Mortality is high in any population that has had little or no experience with measles.

CLINICAL COURSE

The incubation period is generally between 10 and 14 days. In a minority of instances it may be longer (15 to 19 days) or less frequently, it is shorter (less than 10 days). Administration of immune globulin to attenuate the disease after known exposure generally extends the incubation period to as much as 21 days. Infected patients are contagious from 4 days before to 3 days after the onset of rash, but communicability diminishes sharply 48 hours after appearance of rash. Neutralizing antibodies appear simultaneously with the exanthem.

Otitis media is probably the most frequent complication in children. Bacterial pneumonia is the most common lethal complication. Encephalitis occurs in about 1:1000 affected patients in all ages, including the neonate. Most cases of encephalitis occur between 3 and 7 days after the appearance of the rash. The mortality is 10 per cent.

Overall mortality for measles is probably less than 0.1 per cent; but, it is considerably greater in infants younger than 1 year of age.[49]

Maternal Measles During Pregnancy

The incidence of gestational measles before the vaccination era was approximately 0.5 cases per 10,000 pregnancies.[36,38] The incidence has probably diminished considerably since the introduction of vaccine. The naturally low incidence of gestational measles was a function of widespread immunity in adults. Early literature indicates a somewhat higher incidence of complications and death in affected gravida.[49] Pneumonia was the most commonly cited cause of fatality. The epidemic of 1951 in Greenland, although relatively recent, is exceptional because it occurred in a virgin population. Death in affected gravidas was 4.9 per cent versus 1.7 per cent in the nongravid population.[4] In the United States for the past several decades, complications and mortality have been rare.[8]

Effects on the Fetus

There is apparently a higher incidence of prematurity in the presence of gestational measles.[8,38] In Greenland between 1951 and 1962 the rate of abortion was also increased among affected gravida.[16] In the controlled prospective study of Siegel and Fuerst,[38] the increase in prematurity was significant. The report of Gazala et al.[11] described five mothers who delivered premature infants while infected with measles. There was apparently no relationship between measles and abortion.

Gestational measles has not been shown to exert a teratogenic effect on the fetus. The paucity of reported cases and the absence of any discernible pattern of abnormalities, particularly when one considers the frequency of reported epidemics, strongly suggests that the infection is not responsible for fetal malformations. Several studies of epidemics[8,16,39] have failed to demonstrate a teratogenic effect.

Placental transmission apparently occurs, but quite irregularly. Judging from reports of absent neonatal disease in the presence of maternal infection at the time of delivery, placental passage is not frequent. Intrauterine disease has been reported and may be severe, however. Young and Gershon's review of the literature[49] noted a case fatality of 30 to 33 per cent in affected neonates. Mortality among prematures was noted to be higher than among term infants. Pneumonia was the most common cause of death. Most of these reports antedated the availability of antibiotics. Gazala et al.[11] described five mothers whose mean interval from onset of disease to delivery was 3.5 days. All were premature infants; one was a malformed stillbirth. The surviving 4 infants were given 0.2 ml per kg of immune globulin on the day of birth. None of them showed clinical or serologic evidence of measles. In an addendum to their article, the authors describe another infected mother whose premature infant had mild disease at 7 days even though immune globulin was given at birth.

Nursery outbreaks have not been reported, but postnatal acqui-

sition has been described on several occasions.[8,34,49] Dyer's report of 24 infected mothers[8] included 6 who had measles at or near term. Three of their infants recovered after classic clinical measles that began within 2 days of birth. Whether maternal rash was present before, during or after delivery was of no relevance.

SUMMARY

The literature contains reports of epidemics of varying sizes, which in the aggregate suggest that congenital malformations are not attributable to maternal measles infection during pregnancy, that the incidence of prematurity may be somewhat higher among infected mothers, and that the incidence of abortion also may be somewhat higher. Before the introduction of measles vaccine in this country, the universality of childhood experience rendered adult infection a rare event. Gestational measles was thus uncommon. With the introduction of measles vaccine, these numbers can be expected to have decreased substantially.

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Human Parvovirus B19 and Pregnancy

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Human parvovirus B19 (B19) was discovered in 1975 by Cossert et al.[27] while they were evaluating a false-positive result in a counterimmunoelectrophoresis test for hepatitis B virus antigen. The first disease associated with B19 infection was aplastic crisis (AC), in patients with chronic hemolytic anemias such as sickle cell disease.[67, 79] Subsequently, erythema infectiosum (EI) or, fifth disease, in 1983,[8] hydrops fetalis and fetal death in 1984,[13,44] and acute arthritis in 1985[75, 91] were associated with B19 infection. Studies to date have shown B19 to be the primary etiologic agent of AC and EI and associated with some cases of acute arthritis, especially in adults. The link to fetal deaths also has been convincingly shown to be etiologic. The fact that B19 infection during pregnancy can adversely affect the fetus has made it a concern to the pregnant woman and her clinician.

In this review we will discuss the biologic characteristics of the virus and the clinical and epidemiologic features of infection. This information provides the framework within which to consider B19 infection in pregnant women. Although the available information is incomplete, it does allow us to begin to address some of the important questions. For example, which clinical illnesses or epidemiologic situations should suggest B19 infection, what are the risks of an adverse outcome when exposure or infection occurs during pregnancy, which diagnostic tests can be used to evaluate the risks to the pregnant woman and her fetus, and how should one approach the management of the exposed or infected pregnant woman?

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CHARACTERISTICS OF THE VIRUS

B19 belongs to the family Parvoviridae and has been placed in the genus Parvovirus because it does not appear to require a helper virus.[6, 20, 94] Other viruses in this genus include the species-specific bovine parvovirus, feline panleukopenia virus, the canine parvovirus, and the minute virus of mice; these parvoviruses do not infect humans.[84] The genomes of several parvoviruses have been sequenced, and these data show that B19, minute virus of mice, bovine parvovirus, and adenoassociated virus type 2 are genetically distinct but also have regions of significant homology.[18, 80] One region appears to be conserved among the family Parvoviridae and nucleic acid probes to this region may prove useful in identifying and characterizing other human pathogenic parvoviruses. Two new parvoviruses, the RA1 virus[85] and parvovirus-like particles identified in human stool specimens,[68] have been proposed as human pathogens, but neither their role in human disease nor their classification within the family Parvoviridae is yet certain.

Parvoviruses are small, single-stranded DNA viruses that, by electron microscopy, are between 20 and 25 nm in diameter.[21, 27, 30, 86] The single-stranded DNA is about 5.5 kilobases long, and the virus has a buoyant density of 1.39 to 1.45 gm per ml in cesium chloride. Different genotypes of B19 have been identified by restriction endonuclease studies, but no antigenic differences between isolates yet have been reported.[56] The virus encodes for two structural proteins, apparent molecular weights of 58,000 and 84,000, and a major nonstructural protein, apparent molecular weight of 77,000.[28, 66] Since the nonstructural protein is present only in cells with actively replicating virus, its presence can be used to determine sites of replication. No antigenic cross-reactions appear to occur between the structural proteins of B19 and minute virus of mice, the bovine parvovirus, RA1 virus, or the parvovirus-like particles identified in human stool specimens,[29, 68, 80, 85] but antigenic cross-reactions apparently occur between the nonstructural proteins of B19 and the minute virus of mice and the bovine parvovirus.[29, 47, 80]

The virus has not been grown in standard tissue culture systems or animal model systems but can be grown in a bone marrow explant culture system.[60, 65, 66, 94, 95] In this system the virus lytically infects late-stage erythroid precursor cells and is amplified 50- to 200-fold over the input virus.[66] The myeloid series does not appear to be infected. This system has been used to study the structure and replication of the virus but not to amplify virus for diagnostic assays.

DIAGNOSIS

The diagnostic tests available to the clinician and researcher have greatly improved since the early work with electron microscopy and counterimmunoelectrophoresis. The first major diagnostic advance

was the development of an IgM assay in 1982[5] that made it possible to identify recent infection with a single semiacute (several days to 4 weeks after onset of illness) serum specimen rather than with paired, acute- and convalescent-phase serum specimens. This test later was improved with the development of monoclonal antibodies against B19 and their adaptation to capture IgG and IgM radioimmunoassays (RIA)[25] and enzyme-linked immunosorbent assays (ELISA).[3] These tests have proved to be sensitive and specific for detecting recent B19 infection. About 80 to 90 per cent of patients with outbreak-related EI or AC are B19 IgM positive.[3, 5, 25] B19 IgM antibody usually is present by 3 days after onset of illness. The rate of B19 IgM positivity and height of IgM antibody titer begins to fall 30 to 60 days after onset of illness. IgM can persist for 4 months or longer in some persons, but at a low titer. B19 IgG antibody appears a few days after IgM antibody does and persists for many years. In the immunocompetent host, the most sensitive test for recent infection is the RIA or ELISA for B19 IgM antibodies. Presence of B19 IgM antibodies indicates a recent B19 infection (within the last few days to several months, sometimes up to 6 months).

Viral antigens can be detected in serum, body fluids, or unfixed tissues by RIA, ELISA, and immunofluorescence, and B19 DNA by nucleic acid hybridization assays.[3, 7, 22, 25] The hybridization assay is the most sensitive way to detect the virus.[3, 7] With the antigen detection assay, between 20 and 75 per cent of serum specimens collected within a few days after onset of illness from patients with AC will be positive for B19.[3, 4, 67, 73, 79] With the hybridization assay, B19 DNA can be detected up to 1 week after onset of illness in patients with AC.[77] B19 DNA has also been detected in respiratory secretions and urine samples when patients are viremic with B19.[6, 20, 71, 72] B19 antigen and B19 DNA have been detected only rarely in serum specimens from patients with a rash or other non-AC symptoms.[6, 20, 55, 71, 72, 83]

Both light microscopy and electron microscopy have been used to identify tissues likely to be infected with B19. Inclusions that appear to be characteristic of B19 infection have been identified in the nucleus of erythroid progenitor cells in bone marrow explant culture and in a number of tissues from B19-infected fetuses.[2, 94] With transmission electron microscopy, parvovirus-like particles have been demonstrated in intranuclear inclusions of cells infected in vitro and in tissue and tissue homogenates of hydropic fetuses.[12, 94] Neither the inclusions nor parvovirus-like particles are diagnostic of B19 infection, but hybridization techniques can be used to confirm the presence of B19 in the tissue. Nucleic acid hybridization has proved to be a sensitive way to detect B19 in unfixed tissues; recently, it also has been applied to fixed tissues.[23]

To understand the pathogenesis of B19 infection it is also useful to differentiate between presence of the virus (e.g., passively carried through the bloodstream) and active replication. Two techniques can be used to make this distinction: (1) transblot electrophoresis studies to identify the nonstructural proteins indicative of replicating virus,[28]

and (2) Southern blot studies to identify the replicative forms of B19 DNA also indicative of replicating virus.[65]

EPIDEMIOLOGY

The age-specific prevalence of B19 IgG antibodies parallels the age-specific attack rates of EI and AC. EI and AC are primarily illnesses of school-aged children. The prevalence of IgG antibodies increases from 2 to 9 per cent in children less than 5 years old, to 15 to 35 per cent in children 5 to less than 18 years old.[3, 25, 27, 31, 35, 62, 63, 68] In adults, from 30 to 60 per cent have been found positive for B19 IgG; some of these differences are attributable to differences in the sensitivity of the tests used in the studies,[25] some to age differences in the populations tested, and some, probably, to regional differences in infection rates. In outbreaks of EI and among cases of AC no differences in attack rates in children by sex have been observed.[1, 20, 32, 46, 49, 57] In one outbreak of EI, women were more often affected than men.[43] Women also have been reported to have B19-associated arthralgias or arthritis more often than men.[75, 91]

Studies of secondary illness in households have provided very useful information about the incubation period, the rate of asymptomatic infection, and the risk of infection after household exposure.[1, 8, 9, 20, 39, 42, 71] From these studies, the incubation period for clinical EI and AC is usually between 4 and 14 days but can extend to 20 days, and the secondary attack rate for B19 infection among susceptible subjects (persons B19 IgG negative or B19 IgM positive) is 50 to 60 per cent. Among susceptible subjects, the secondary attack rate varies little with age. In household contacts with B19 infection (B19 IgM positive), 50 to 60 per cent reported having a nonrash illness, including 15 to 25 per cent that reported no symptoms associated with infection.[20, 71] Thus, about 50 per cent would not have been diagnosed as having a B19 infection on clinical grounds. On the basis of clinical illness, between 10 and 60 per cent of students in schools with EI outbreaks become infected.[1, 8, 46]

Outbreaks of EI last from 2 to 6 months, often beginning in mid- to late winter and continuing until school recesses for the summer.[1, 8, 20, 39, 46, 71] EI and AC, however, can occur throughout the year. Because the presence of EI in schools is our best indicator of B19 activity in a community, we have little information about community outbreaks once schools close for the summer. EI activity appears to be cyclical, with peak activity occurring every 5 to 7 years in a community.[19]

As noted above, B19 DNA has been identified in respiratory secretions from persons with clinical AC while they are viremic, in volunteers experimentally infected with B19, and in persons with natural infection but before they developed symptoms consistent with B19 infection.[6, 20, 71, 72] B19 has rarely been identified in persons while they have a non-AC illness.[55] These findings suggest that respiratory

secretions are involved in the transmission of B19. The findings also suggest that persons with EI are not likely to be infectious once the rash develops or within a few days thereafter; persons with AC, on the other hand, are likely to be infectious at the onset of illness and up to a week later.

CLINICAL CHARACTERISTICS OF B19 INFECTION

Erythema Infectiosum (Fifth Disease)

EI was first associated with B19 infection by Anderson et al. during an outbreak in England.[8] Since this report, multiple outbreaks of EI, as well as outbreaks of rash illness atypical of EI, have been associated with B19 infection.[3, 8, 48, 62, 63, 71, 76, 81] It is now clear that B19 infection is the primary etiologic agent of EI. Typically EI occurs in school-aged children as a facial rash ("slapped cheek" appearance) that spreads to the extremities and trunk, often with a reticulated (lace) pattern. The rash is usually macular and can have a variety of features, including being morbilliform, confluent, circinate, vesicular, and purpuric.[1, 9, 17, 26, 32, 42, 69, 74, 88] In two recent outbreaks,[32, 77] rash has been noted on the palms and soles. Recurrences of the rash often are noted and can be precipitated by several stimuli, including changes in temperature, sunlight, and emotional stress. In up to 60 per cent of patients the rash is preceded by 1 to 4 days of fever, malaise, myalgias, upper respiratory symptoms, or gastrointestinal symptoms; most patients feel well by the time the rash develops. Pruritus has occurred frequently in some but not all outbreaks. Adults also can develop a typical EI-like illness but are more likely to also have arthralgias or arthritis.[1]

Aplastic Crisis

AC was the first illness associated with B19 infection.[67, 79] As with EI, subsequent reports have confirmed B19 as the principal etiologic agent of AC in persons with a variety of chronic hemolytic anemias, including sickle cell disease, hemoglobin SC disease, hereditary spherocytosis, thalassemia, pyruvate kinase deficiency, and acquired hemolytic anemias.[4, 11, 15, 33, 34, 38, 41, 48, 49, 57, 61, 73, 77, 78, 90] Patients with AC often consult their physician with symptoms of lethargy and pallor and usually have a history of a viral-like illness that began 1 to 7 days earlier. Some, fewer than 25 per cent, of patients have been reported to have a rash. The characteristic laboratory finding in people tested early in their illness is a moderate to severe anemia and absence of reticulocytes.[4, 11, 15, 33, 34, 38, 41, 49, 57, 73, 77, 78, 90] Bone marrow examination at onset of illness shows a hypoplastic or aplastic erythroid series and normal myeloid series.

The reticulocytopenia and hypoplastic erythroid series in the bone marrow are consistent with the finding that B19 selectively infects erythroid precursor cells in vitro. Experimentally infected volunteers with normal red blood cell turnover also experienced a reti-

culocytopenia and decrease in hemoglobin beginning 7 to 11 days after inoculation. The reticulocyte count returned to normal 10 to 14 days later.[6, 72] Along with the red cell aplasia, the volunteers experienced transient neutropenia, lymphocytopenia, and thrombocytopenia the second week after inoculation. These studies suggest that red cell aplasia is a consistent feature of B19 infection but usually is not detected in persons with a normal red blood cell turnover time and that abnormalities of the white blood cells and platelets are common but often not detected.

Arthritis

Arthralgias and arthritis have been common features of EI in adults but not in children. In one study, 59.6 per cent of adults but only 2.8 per cent of children had acute joint swelling.[1] In a study that examined the clinical characteristics of 30 patients with B19-associated arthritis, the peripheral joints were most commonly affected and usually symmetrically.[75] The symptoms usually resolved within 2 weeks, but in two patients symptoms persisted for 6.5 and 24 weeks, respectively. About half had an associated rash illness that usually was present before but sometimes appeared after the arthritis. In a study of patients attending an early synovitis clinic, 19 of 153 (12 per cent) had evidence of recent B19 infection (B19 IgM antibodies) and 3 of the 19 had persistence of symptoms for over 4 years.[91] Several groups have studied B19 infection in patients with rheumatoid arthritis and found a tendency for cases to have a higher rate of B19 IgG antibodies (past infection) or B19 IgM antibodies (recent infection) than controls.[24, 53]

B19 Infection in Immunosuppressed Patients

Chronic B19 infection with an associated chronic red blood cell aplasia or a more generalized bone marrow failure has been demonstrated in a patient receiving immunosuppressive chemotherapy and a patient with severe combined immunodeficiency syndrome.[45, 87] These two cases suggest that B19 should be considered in the differential diagnosis of both acute and chronic red blood cell aplasia in patients who are immunosuppressed.

Other Diseases

Case reports have documented recent B19 infection in patients with Henoch-Schönlein purpura and encephalitis and pneumonia in patients with EI.[10, 40, 50, 51, 59, 69] An etiologic link between B19 infection and these clinical syndromes has not been confirmed.

B19 INFECTION AND PREGNANCY

B19 Infection and Fetal Death

Since first reported in 1984, the link between B19 infection and fetal death has been convincingly demonstrated to be causal. This link

is suggested by the reports of high-titered B19 DNA in multiple tissues from nine abortuses and by a consistent pathologic picture of hydrops fetalis.[2, 12, 16, 70, 89, 92] However, most of the over 170 cases reported in the literature of B19 infection during pregnancy have led to no abnormalities in the infants.[2, 12–14, 16, 36, 44, 52, 58, 70, 83, 89, 92, 93]

The pathogenesis of fetal death appears to be similar to that for AC in persons with increased red blood cell turnover. The selective cytopathic infection of red blood cell precursors presumably arrests red blood cell production, which, because of a shortened cell survival and expanding cell volume, causes a severe anemia.[37] The severe anemia in turn causes congestive heart failure, generalized edema, and death, a clinicopathologic picture consistent with nonimmune hydrops fetalis. This scenario for the pathogenesis of B19 disease in the fetus is supported by the one report of reticulocytopenia and severe anemia in a blood sample from a B19-infected fetus taken shortly before the fetus died[16] and the presence of nuclear inclusions in red blood cell precursors of B19-infected fetuses.[2, 16] The report of an aborted, B19-infected fetus with anomalies of the eye suggests that a cytopathic infection may occur in tissues other than those that are hematopoietic tissues.[89]

B19 Infection and Congenital Anomalies

Another concern regarding B19 infection and pregnancy is that it may cause congenital anomalies. The fact that the species-specific parvoviruses are teratogenic[84] and that one aborted fetus had evidence of B19-related anomalies of the eye suggests that this may happen.[89] However, among the over 130 liveborn infants of B19-infected mothers reported in the literature, none has had a congenital anomaly[2, 12–14, 16, 36, 44, 52, 58, 70, 83, 89, 92, 93]; this suggests that if B19 infection in the mother does cause congenital anomalies, it does so infrequently.

Risk of Fetal Death after B19 Infection

Several recent studies have provided limited data about the importance of B19 as a cause of fetal death and the risk of fetal death after exposure to B19-infected persons. Preliminary results from a study in England provide the only data from which to make an estimate of the risk of fetal death after B19 infection. In this study, 134 pregnant women with a B19-like clinical illness and serologic evidence of recent infection (positive for B19 IgM antibodies) were followed prospectively. Among 46 women with illness during the first 9 weeks of pregnancy, 7 (15 per cent) had fetal death; among 66 women with illness during 10 to 18 weeks of pregnancy, 11 (17 per cent) had fetal death; and among 13 women with illness during 19 to 27 weeks of pregnancy, none (0 per cent) had fetal death. Three of the ten fetuses tested for B19 DNA showed positive results. The lack of a control group and adequate data on rates of fetal death during the first 20 weeks of pregnancy make it difficult to determine how many of these deaths were caused by B19 and how many were caused by other factors. However, the rate of fetal loss, particularly among women with

illness at 10 to 18 weeks' gestation, does appear to be high. In one study, the fetal death rate was 7 per cent from 12 weeks' gestation to delivery.[82] Despite the limitations of the English study, its results do provide a rough estimate of the rate of B19-related fetal deaths among infected women and suggest that the rate is greatest during the first 18 weeks of pregnancy. If we assume that the rate of B19 DNA positivity in the aborted fetuses (30 per cent) gives the per cent of fetal deaths attributable to B19, then about 5 per cent of women infected during the first 18 weeks of pregnancy lost their pregnancy because of the infection. The true rate may be higher or lower but is certainly less than the rate of 16 per cent we would obtain if all deaths were attributed to B19.

Why some infections during pregnancy lead to fetal death and others do not is unclear. In some instances the fetus does not become infected, as suggested, by the lack of B19 IgG antibodies at 12 to 15 months of age in 12 infants born of B19-infected women.[58, 70] In other instances the fetus does become infected with no apparent adverse effect. For example, 9 normal infants born of B19-infected women have been reported to have serologic evidence of intrauterine infection, 4 had B19 IgM antibodies in cord blood, and 5 had B19 IgG antibodies present in serum at 9 to 16 months of age.[58, 70, 92]

A study by Kinney et al.[43] provides information about the importance of B19 infection as a cause of fetal death among the general population of pregnant women. In this case/control study of women with stillbirths (fetal death at ≥20 weeks' gestation) or spontaneous abortions (fetal death at <20 weeks' gestation), 0 of 96 cases and 1 of 96 controls and 2 of 96 cases and 1 of 96 controls, respectively, had evidence of B19 infection during their pregnancies. These results suggest that among an unselected population of pregnant women, B19 infection is uncommon and an uncommon cause of fetal death.

The last set of studies provides data on the rate of infection after household and school exposure. The secondary attack rate of B19 infection (B19 IgM positive) after exposure to a household member with EI suggests that about 50 per cent of susceptible adults will become infected.[20] If we assume that the true rate of fetal death from B19 is 5 per cent following maternal infection, then the rate of fetal death for susceptible women after household exposure during the first 18 weeks of pregnancy would be about 2.5 per cent. The attack rate of B19 infection among susceptible teachers working in the schools with EI outbreaks was about 15 per cent in one study (Centers for Disease Control. Unpublished data, 1987); a rate lower than that after household exposure. At this rate of infection, a pregnant susceptible teacher working in a school with an EI outbreak would have a risk of a B19-related fetal death substantially lower than the 2.5 per cent estimate for women exposed at home.

Approach to B19 Infection During Pregnancy

The available data suggest that B19 infection should only be a concern to the pregnant women under two circumstances: (1) when

she is exposed to B19 infection, or (2) when she develops an illness suggestive of B19 infection. These data also suggest that most women under either circumstance will have no adverse outcome and that the risk of an adverse outcome is likely to be greatest when exposure and infection occur during the first 18 weeks of the pregnancy.

We have been consulted most often regarding two types of exposure to B19 infection, namely, household and school. The risks after these types of exposure have been outlined previously. In considering these exposures, it is important to remember that once the rash develops, the greatest risk of transmission has already occurred, and the EI patient is not likely to present a substantial additional risk to the women. Preventing additional exposure in the home is often not practical; preventing additional exposure in the schools with ongoing outbreaks of EI may be possible. Some health department officials have recommended that teachers in schools with EI stay home from work during the outbreak; others have not recommended this. Unfortunately, school outbreaks may begin in January or February and continue until school recesses for the summer (a long time for the teacher to be out of work), and no approach to preventing infection or fetal death after exposure has been studied. In considering management options, it is helpful to determine the B19 IgG status of the pregnant women. (Antibody testing can be obtained by consulting your state health department and Drs. W. G. Gary or L. J. Anderson, Division of Viral Diseases, Centers for Disease Control, Atlanta, Georgia.) Given our current level of understanding, the IgG-positive woman is presumed not to be susceptible and the IgG-negative woman is presumed to be susceptible. No formal recommendations have been established regarding the approach to the pregnant, susceptible woman with continued exposure to B19. The estimates of risk noted previously provide the basis for the pregnant woman and her physician, in consultation with public health officials, to consider the options. If the pregnant woman develops an illness suggestive of B19 infection, then it is reasonable to document the infection and follow the status of her fetus as noted below. Illnesses most suggestive of B19 infection are EI, AC, and acute arthritis, but about 50 per cent of B19-infected persons will have atypical symptoms and up to 25 per cent will be asymptomatic.[20, 71] Women with stillborn or aborted fetuses have been reported to have rash illnesses, arthritis, and no symptoms associated with infection.[2, 12, 16, 83, 89, 92]

Management of pregnant women with clinical illnesses suggestive of B19 infection, including EI, AC, and acute arthritis, should include documentation of infection by IgG and IgM antibody tests. The risk of fetal death with infection, as noted previously, probably is greatest during the first half of pregnancy. However, there is one report of fetal death at 40 weeks' gestation and, although the time of infection was unknown, it presumably occurred in the second half of pregnancy.[44] Fetal death has been reported to occur from 1 to 10 weeks after clinical illness in the mother.[2, 12, 58, 70, 83, 92]

The fetus of a B19-infected mother can be monitored by ultra-

sound and maternal serum alpha-fetoprotein (MsAFP) levels.[2, 16] In one study, MsAFP levels were elevated in women who subsequently aborted B19-infected fetuses; MsAFP levels were not elevated in women who delivered normal infants.[16] Elevations in MsAFP have been noted up to 6 weeks before fetal death and 4 weeks before abnormalities were apparent by ultrasound. Fetal edema and ascites have been noted by ultrasound up to 2 weeks before fetal death. Intrauterine blood transfusions have been proposed as a treatment for the fetus with a B19-induced severe anemia.[16]

CONCLUSIONS

Despite limited data, it is now possible to make rough estimates of the risk of B19-related fetal death after both exposure and documented infection in the mother. In both cases most fetuses will not be affected. B19 serologic tests, ultrasound, and alpha-fetoprotein levels can be used to aid the clinician in managing the exposed or infected patient. Further study, however, is needed to define management options more clearly. Some areas for future study include determining the rate of infection after different types of exposures and the rate of fetal death following maternal infection, determining if and how often a fetus with evidence of intrauterine B19 infection will develop a congenital anomaly if it survives the infection, and evaluating ways to prevent (e.g., prophylactic use of immune globulin in women with ongoing exposure to B19) and treat (e.g., intrauterine blood transfusions) this disease.

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Gestational and Congenital Syphilis

*George D. Wendel, MD**

Despite descriptions of neonatal infection for over 450 years and the availability of adequate therapy for over 40 years, antepartum and congenital infection from *Treponema pallidum* remains a significant concern for perinatal care providers. After many years of low rates of congenital syphilis in the United States, health care workers are again faced with the resurgence of this infection due to marked increases in primary and secondary syphilis in some areas of the country.[12] Additionally, some of the recently reported cases of congenital infection have been delivered of women who obtained prenatal care or who were treatment failures.[11] Concern over the role of genital ulcers in facilitation of human immunodeficiency virus (HIV) infections has emphasized the potential role of syphilis in this worldwide epidemic. Cases of advanced progression of syphilis[37] and treatment failure[3] in patients with HIV infections have also raised concerns about possible alterations of the natural history of syphilis in that population. Collectively these findings have focused attention on the possibility of an increased incidence of syphilis in heterosexuals likely heralding the return of congenital syphilis.

EPIDEMIOLOGY

The incidence of primary and secondary (P and S) syphilis in the United States steadily increased from 1977 to 1982 when it reached 14.6 cases per 100,000,[10] but it has gradually declined to a rate of 11.4 per 100,000 by 1986.[10,11,13] This change in the rates of P and S syphilis was due to the large decrease in rates for male subjects, especially those who are homosexual. Overall, from 1977 to 1984 the rates of P and S syphilis have increased 26 per cent for men and 43 per cent for women, but there were almost 2.5 times as many cases in men as in women.[8] Alarmingly, there has been a 23 per cent increase in P and S syphilis in the United States in the first quarter of 1987 compared

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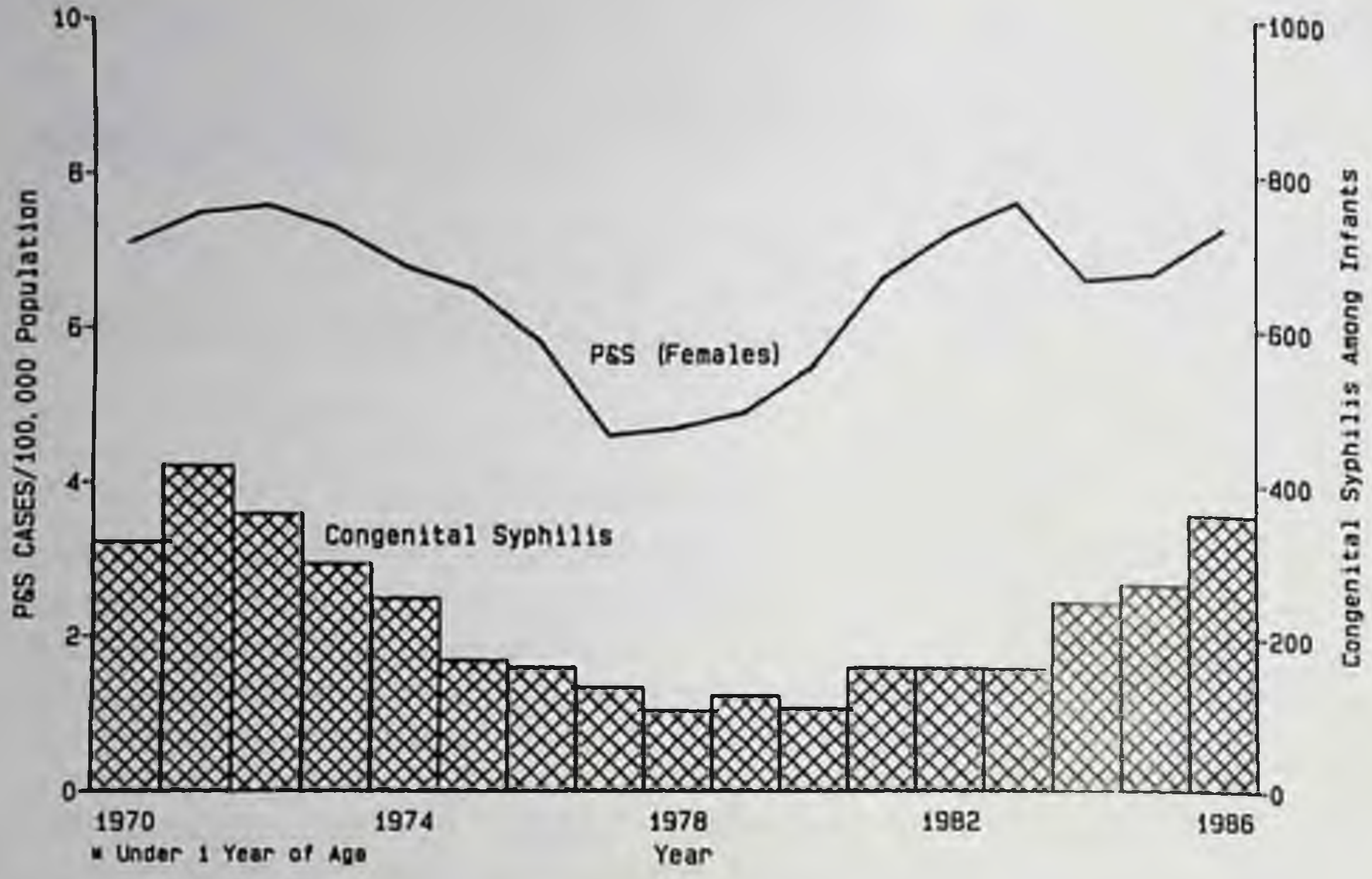

Figure 1. Case rates of primary and secondary (P&S) syphilis among females and congenital syphilis (in infants less than 1 year of age) in the United States, 1970–1986. (*From* Centers for Disease Control: 9.688: CDC, Atlanta, Public Health Service, 1987, with permission.)

to the same quarter of 1986.[12] These increases were greatest in New York City, Florida, and California and occurred in heterosexual populations with an over-representation of cases in women.

The increasing rates of P and S syphilis in women have led to a dramatic rise in the number of cases of congenital syphilis detected at less than 1 year of age. From 1980 to 1986 the number of cases has increased from 111 cases to 365 cases per year (Fig. 1).[11,13] Similar trends are certain to be noted for the next several years because increases in congenital syphilis rates are often reflective of the prior year's rates for P and S syphilis in women. Not surprisingly, large urban areas and large states such as Texas, Florida, and California account for almost three fourths of the cases of congenital syphilis annually.[11] In 1985, Texas reported 17 per cent of the cases of P and S syphilis and 31 per cent of the congenital syphilis detected at less than 1 year of age in the United States.[11,76]

From 1980 to 1985, Dallas County consistently has reported 5 to 6 per cent of the total cases of congenital syphilis in the United States.[76] In 1985, Dallas County reported 1740 cases of P and S syphilis (6.5 per cent U.S. total) and had a rate of 76.9 cases of P and S per 100,000 population.[76] The county also had a P and S rate of 214 cases per 100,000 in the highly fertile 20 to 29-year-old age group. At Parkland Memorial Hospital in Dallas County, approximately 2 per cent of the pregnant patients have reactive serologic tests for syphilis, and

there have been 1.2 cases of congenital syphilis per 1000 births over the past 2 years (27,568 deliveries).[42]

Numerous studies have described the epidemiology of antepartum and congenital syphilis in the United States.[26,48] They are diseases of women who receive inadequate prenatal care. The mothers are young, unmarried, from lower socioeconomic background and have little, late, or no prenatal care. The Centers for Disease Control (CDC) reported that of 437 infants with congenital syphilis born from 1983 to 1985, only 52 per cent were delivered from women with prenatal care.[11] The mean age of first prenatal visit was 22 weeks in this group. Unfortunately, almost half of the cases of congenital infection in the women with prenatal care may have been preventable due to failures to do initial or third trimester serologic screening and failure to treat infection in high prevalence areas. It is worrisome that treatment failures accounted for 19 per cent of the total cases and 35 per cent of the cases in women who had prenatal care. Thus, the underutilization, timing, and content of prenatal care all are contributing factors in these cases.

EFFECT OF PREGNANCY ON SYPHILIS

Serologic Tests for Syphilis

The diagnosis of antepartum syphilis is most often made by serologic screening done at the first prenatal visit. This has been shown to be cost effective even in models of low prevalence areas, where the incidence of syphilis might be 5 per 100,000.[71] Serologic screening usually involves nontreponemal tests such as the Venereal Disease Research Laboratory (VDRL) or Rapid Plasma Reagin (RPR) tests, which measure anticardiolipin antibody.[32,41] These tests are reactive in almost all patients with secondary and early latent (less than 1 year's duration) and in about 80 per cent of patients at their initial visit for primary syphilis.[54] These tests are reported as non-reactive, weakly reactive, or with a titer. Higher titers generally reflect active disease with clinically detectable involvement and tend to be highest with secondary syphilis, somewhat lower with primary disease and lowest with latent infection. Reactive nontreponemal tests are usually confirmed by specific antitreponemal antibody tests such as the Microhemagglutination Assay for Antibodies to *T. pallidum* (MHA-TP) and the Fluorescent Treponemal Antibody–Absorption (FTA-ABS) test.[32,41] These tests are reported as reactive or nonreactive and generally not given titers.

Interpretation of quantitative titers of the nontreponemal tests and qualitative treponemal test results are important in difficult diagnostic situations in pregnancy and for followup after therapy.[32,41] False-positive serologies are those with reactive nontreponemal tests, but without specific antitreponemal antibody. These are usually transient and of low titer. They can follow systemic febrile illnesses or be due to

laboratory error. Chronic false-positive serologies occur in 1 to 2 per cent of cases and should raise suspicions about active intravenous drug abuse or subclinical autoimmune disease.[52] Pregnancy is described as a cause of false-positive serologies, but published reports are conflicting in pregnancy's effect on the specificity of syphilis serologies.[52,47] Nontreponemal test titers usually decrease fourfold by 3 months after therapy in nonpregnant adults,[6] but treponemal test results remain positive for life. These titers can be used to monitor serologic response to therapy during pregnancy or assess adequacy of prior treatment.

Clinical Diagnosis

Pregnancy has no known effect on the clinical course of syphilis, but missed or erroneous diagnoses can occur. The diagnosis of asymptomatic reinfection is difficult to rule out with an increased VDRL titer and a history of prior therapy. Most women at the Obstetrical Complications Clinic at Parkland Memorial Hospital are diagnosed with early latent, secondary, latent of unknown duration, or primary syphilis in decreasing order of frequency. Using careful speculum examination, some of these women can be shown to have cervical chancres.[82] The cervical hyperemia, eversion, and friability of pregnancy may make this area an easy portal of entry for *T. pallidum* that often goes undetected. Other common complaints of pregnant women may be subtle signs of the great imitator, secondary syphilis. Alopecia, palmar erythema, diffuse dermatoses, and low-grade fever with malaise have all been presenting symptoms of syphilis that have been misdiagnosed as physiologic changes of pregnancy. In high prevalence areas, serologic testing for syphilis should be considered with those complaints. Additionally, other sexually transmitted diseases may mimic the lesions of secondary syphilis or be present as a coinfection. Women with inguinal adenopathy or suspected condyloma acuminata, genital herpes, chancroid, lymphogranuloma venereum, and cervical flat condylomas all should be evaluated for syphilis if the presentation is atypical or the laboratory evaluation negative.

EFFECT OF SYPHILIS ON PREGNANCY

Fetal Infection

Untreated syphilis can profoundly affect pregnancy outcome since treponemes appear to be able to cross the placenta at any time during pregnancy. *T. pallidum* was detected by silver staining and immunofluorescent techniques in first trimester abortion specimens in one report,[33] but undetectable in fetuses younger than 18 weeks' gestation in a prior report.[19] It has been hypothesized that fetal immunoincompetence explains the lack of clinical involvement and high success of treatment noted prior to 16 to 18 weeks' gestation.[65]

Syphilis may cause preterm delivery, stillbirth, congenital infec-

tion, or neonatal death depending on the stage of maternal infection and the duration of fetal infection prior to delivery. Rates of congenital infection are related to the duration of maternal infection and degree of spirochetemia. Most infants who congenitally are infected are born to women with early syphilis.[25] Recent or current secondary infection confers the greatest risk, as it is typified by a large, systemic organism load. Low birth weight is common with symptomatic infants due to preterm delivery.[50] The mechanism by which this hematogenously acquired fetoplacental infection initiates preterm labor is not presently understood. With untreated first and second trimester infection, significant fetal morbidity can be expected, but with third trimester infection many infants are asymptomatically infected. Virtually all infants born to women with P and S syphilis will have congenital infection, 50 per cent will be clinically symptomatic.[25] The incidence of infection drops to 40 per cent with early latent and to 6 to 14 per cent with late latent stages.[25]

Infection *in utero* may lead to fetal demise, presumably from overwhelming fetoplacental involvement. From 1983 to 1985, the percentage of stillborn congenital syphilis cases increased from 19 to 29 per cent.[11] At Parkland Memorial Hospital almost half of the cases of congenital syphilis were stillborn in 1986.[42] The increases may be from improved evaluation and reporting of stillbirths, but underscore the preventive value of prenatal care. Neonatal mortality may be as high as 54 per cent in affected infants.[35] Some of the perinatal mortality in congenital syphilis may be related to prematurity and not be preventable by neonatal treatment.

Clinical Diagnosis

The CDC have adopted a set of clinical and serologic criteria that is useful for reporting cases of congenital syphilis with varying degrees of certainty of diagnosis.[39] It can be used to classify disease into definite, probable, possible, and unlikely categories for reporting and followup. Since most states require serologic screening in pregnancy, which usually is performed at delivery, attention is focused on diagnosing neonatal infection prior to discharge from the hospital.

Neonates generally do not have signs of primary syphilis when infection was acquired *in utero* from hematogenous spread across the placenta. Their manifestations are systemic, similar to those in adults with secondary syphilis, with an additional 40 to 60 per cent chance for central nervous system involvement.[35,53] The most common findings in the neonatal period are hepatosplenomegaly, jaundice, and osteochondritis; and they differ from those detected in infants over one month of age (Table 1).[35] Congenital syphilis is the most common cause for nonimmune hydrops at Parkland Memorial Hospital and should be strongly considered in the differential diagnosis in other high prevalence areas. Other neonatal signs can be lymphadenopathy, pneumonitis, myocarditis, nephrosis, and pseudoparalysis.[39,53] Third trimester infection can result in asymptomatic or incubating

Table 1. *Clinical Features of Early Congenital Syphilis*

FEATURE	AGE < 4 WEEKS (%)	AGE > 4 WEEKS (%)
Hepatosplenomegaly	91	87
Joint swellings	3	34
Skin rash	31	55
Anemia	64	89
Jaundice	49	7
Snuffles	12	50
Metaphyseal dystrophy	95	91
Periostitis	37	80
Cerebrospinal fluid changes	44	37

Adapted from Hira SK, Bhat GJ, Patel JB et al: Early congenital syphilis: Clinicoradiologic features in 202 patients. Sex Transm Dis 12:177, 1985.

infection; such infants should be treated for presumed congenital syphilis.

Laboratory Diagnosis

Lumbar puncture for cerebrospinal fluid analysis and long-bone radiography[17,35] are essential in any neonate whose mother was not adequately treated before 16 to 18 weeks' gestation. Unfortunately, the diagnosis of congenital neurosyphilis is hampered by nonspecific cerebrospinal fluid (CSF) cytologic and chemical findings and inconsistent serologic tests.[68,78] Despite its insensitivity, a CSF VDRL should be obtained in any symptomatic or asymptomatic infant prior to therapy as a baseline for followup.[9] Radiographic changes such as metaphyseal dystrophy, osteitis, and periosteal reaction are present in over 95 per cent of affected neonates.[35] Although these radiologic findings are consistent diagnostic features in these infants and indicate congenital infection, they are not specific for congenital syphilis. Osteochondritis is associated with recent fetal infection (approximately 5 weeks), and periostitis represents prolonged involvement (approximately 16 weeks), usually suggesting second trimester infection.[53]

All stillbirths should have a whole-body radiographic survey,[17,18] and autopsy,[58] if possible. Stillborn specimens are often autolyzed, obscuring the histopathologic diagnosis of congenital infection, but osteochondritis is visible radiographically in clinically affected fetuses.[16,18] Additionally, dark-field examination and histopathology of the umbilical cord, placenta, and moist skin lesions may aid in the diagnosis. Spirochetes may be detected with silver staining techniques[58] or immunofluorescence[23] in fetal tissue.

Placental involvement may be manifest grossly by a large, pale, waxy, hydropic placenta. Spirochetes may be visualized microscopically with special staining techniques.[20,33,62] A histologic triad of focal villitis, endovascular and perivascular proliferation in villous vessels, and relative immaturity of villi has been described.[62]

Interpretation of positive serologic tests for syphilis on sera obtained from the cord blood or preferably the neonate is complicated by the transplacental transfer of maternal IgG antibody. Uninfected infants may possess maternally acquired antibodies at concentrations comparable to those of neonates infected with *T. pallidum*. VDRL antibody titers at least two dilutions (fourfold) higher than the maternal VDRL titer indicate probable fetal infection.[39] IgM antibody does not cross the placenta, and levels in newborns should reflect fetal antibody production. Unfortunately, neonatal total IgM concentrations and specific fluorescent treponemal IgM (FTA-ABS IgM) tests employed as diagnostic tests for congenital syphilis have not been reliable.[2,38,46] Conversely, neonatal serologies may be nonreactive with incubating congenital syphilis from peripartum maternal infection.

PREVENTION OF CONGENITAL SYPHILIS

Prenatal Care

The diagnosis and treatment of syphilis in pregnant women is almost completely dependent on the availability and utilization of adequate prenatal care.[31,48,61] Early and rapid entry into comprehensive prenatal care programs is essential in high-risk populations for STDs and in areas with a high incidence of P and S syphilis. Serologic screening should be done at the first prenatal visit with a thorough physical examination, including attention to signs of sexually transmitted diseases. In high-risk settings, the serologic screening should be repeated at 28 weeks' gestation and at delivery. Such systems will help detect latent or undiagnosed early syphilis that has occurred since the initial examination. Serologic screening is economically cost effective in preventing congenital syphilis, even when the incidence of maternal syphilis is as low as 5 cases per 100,000 women.[71] The use of medical records from family planning clinics, STD clinics, hospitals, and drug treatment facilities often aid in documentation of duration of disease, prior serologies, or therapy. This is particularly helpful in evaluating women with latent infection or serofast serologies with a history of treatment. High-quality prenatal care, especially in high prevalence areas, must include early intervention by providers who are well informed about serologic screening, clinical detection, treatment and followup of syphilis in pregnancy.[31,81]

Penicillin

Parenteral long-acting benzathine penicillin G remains the drug of choice for treating maternal infection and preventing fetal infection. The efficacy in treatment of early syphilis (delivery of an unaffected neonate) is approximately 98 per cent, barring reinfection or therapy late in pregnancy.[36,77] The CDC-recommended schedules for therapy of the pregnant woman were last updated in 1985 and are similar to those for nonpregnant adults (Table 2).[9]

Table 2. *Recommendations for Treatment of Syphilis in Pregnancy*

Early syphilis
(Primary, secondary, latent syphilis of less than 1 year's duration)
Benzathine penicillin G 2.4 million units IM at a single session
Syphilis of more than 1 year's duration
(Latent syphilis of unknown or more than 1 year's duration, cardiovascular or late benign)
Benzathine penicillin G 2.4 million units IM weekly for 3 successive weeks.
Neurosyphilis
Potentially effective regimens include 6.0–9.0 million units of penicillin G over 3–4 weeks. Specific guidelines are in MMWR 34(45):23, 1985

Many prospective studies have addressed the treatment of nonpregnant adults[64]; however, there are few published evaluations on the efficacy of therapy in pregnancy. No prospective, randomized evaluation of even the CDC-recommended dosage regimens has assessed maternal response to therapy and efficacy in preventing/curing fetal infection.[5,77] Of particular concern is the lack of information concerning therapy of gravidas in the late second and third trimester, when most therapeutic failures (delivery of an affected neonate) occur.[11,49] Altered penicillin pharmacokinetics may occur due to changes in renal clearance and plasma volume that are normal adaptations in pregnancy. Recent secondary syphilis also increases the chance for treatment failure, possibly due to a greater organism load or a greater chance for severe, irreversible fetal infection. Understanding of the fetal response to infection or therapy also has been hampered by lack of an objective means to identify the congenitally infected fetus or follow its response to therapy. Additionally, there is no animal model to investigate treatment of fetal infection with *T. pallidum*.

Erythromycin

Patients with syphilis and a history of penicillin allergy (prevalence 5 to 10 per cent), require consideration of alternative drugs and a switch to an oral regimen of 15 to 30 days, depending on the stage of the disease. Neither of the drugs recommended by the CDC for treating penicillin-allergic subjects, tetracycline or erythromycin,[9] has been evaluated extensively in pregnancy.[77]

The usual alternative antibiotic, erythromycin, has a cure rate of only 90 per cent in adults with early syphilis at 1 year post-therapy[64] and may be less effective with disease of greater than 1 year's duration.[9] Recent reports of congenital syphilis after erythromycin therapy[11,49,24,34,46,67] have strongly questioned its use in pregnancy. None have adequately determined strict compliance to the oral therapeutic regimen. More importantly, a recent report describes a strain of *T. pallidum* that is resistant to erythromycin in an in vitro system

Table 3. *Recommendations for Treatment of Syphilis in Penicillin Allergic Patients*

Confirm Penicillin Allergy
1) Document penicillin allergy history (pruritus, urticaria, dyspnea, bronchospasm, anaphylaxis)
2) Skin testing: major and minor determinant antigens
Recommended Regimen
1) Offer desensitization followed by appropriate penicillin dosage for stage of syphilis.
Alternative Regimen
1) Erythromycin, 500 mg qid, orally for 15 days (early syphilis).
2) Tetracycline, 500 mg qid, orally for 15 days (early syphilis).
3) Non-penicillin therapy for disease of greater than one year's duration *not* recommended.
Asymptomatic infants born to women treated with nonpenicillin regimens should be treated with benzathine penicillin G, 50,000 units/kg intramuscularly in a single dose.

measuring inhibition of protein synthesis by various antibiotics.[69] Additionally, the presence of plasmid DNA in Nichols strain *T. pallidum* suggests the potential for the development of plasmid-mediated resistance.[56]

Both erythromycin base and stearate are acid labile and susceptible to decreased absorption from exposure to acidic gastric contents[79] that may be increased from delayed gastric emptying in pregnancy. Enteric-coated base preparations that are protected from upper gastrointestinal acid degradation have better bioavailability and may be a better choice in pregnancy.[28] Although efficacy of erythromycin therapy is an important concern in the gravida with syphilis, noncompliance from untoward effects may even be a greater obstacle.[6,41] Seven of eight penicillin-allergic patients with syphilis at Parkland Memorial Hospital treated initially with oral erythromycin base or stearate were noncompliant due to gastrointestinal complaints.[80] Several other reports have shown unpredictable maternal serum levels and transplacental transfer of erythromycin[40,60] to further compound the problem of treating maternal–fetal syphilis. Accordingly, CDC recommendations call for penicillin therapy for neonates delivered of erythromycin-treated mothers, as they may be inadequately treated *in utero* (Table 3).[9]

Tetracycline

Tetracycline use in pregnancy has been avoided because of staining of decidual teeth[29] and temporary impairment of long-bone growth.[14] However, there have been no demonstrable long-term side effects on rates of dental caries, enamel hypoplasia, or skeletal development in children followed to age 5 to 6 whose mothers received oral tetracycline for up to 6 weeks for asymptomatic bacteriuria during

pregnancy.[22] It is of proven efficacy in treating infectious syphilis in adults,[26] but limited data are available concerning its efficacy in pregnancy.[77] Tetracycline also is plagued by the need for prolonged compliance and has been associated with gastrointestinal side effects[63,64] as well as hepatic toxicity in pregnancy when used in patients with impaired renal function.[83]

Doxycycline has been studied in nonpregnant adults with good response in infectious syphilis.[57] It binds calcium less than other tetracyclines, and caused enamel staining in only 4 per cent of premature infants treated at birth who were followed up at 1 year.[27]

Cephalosporins and Chloramphenicol

Cephalosporins and chloramphenicol have been evaluated in uncontrolled, limited series in pregnancy.[77] Cephalosporins would be acceptable alternatives to penicillin therapy, and have been effective in treating experimental animals[45] and adults.[21,55] The use of cephalosporins would likely require prolonged oral or parenteral administration for 1 to 2 weeks, and thus compound the problem of compliance with excessive cost. Additionally, immunologic and clinical cross-reactivity exists among the family of beta-lactam antimicrobials.[72–74] While the risk of an allergic reaction to cephalosporins is low in penicillin-allergic patients,[66] serious reactions and deaths have been reported.[74] Therefore, these drugs should not be routinely substituted for penicillin in this group of allergic patients.

Penicillin Allergy

Approximately 7 per cent of patients report a history of an allergic reaction to penicillin, most frequently urticaria, pruritus, or shortness of breath. Skin testing enables the physician to identify the 2 per cent of patients with IgE who are at risk for acute allergic reactions to penicillin.[72] The presence of IgE to the major determinant antigen, penicilloyl polylysine and to the minor determinant antigens, benzylpenicillin G and penicilloic acid, identifies this group. Patients with positive skin tests have a risk of acute allergic reaction of approximately 40 to 75 per cent.[30,43,59] Persons with minor determinant reactivity may be at higher risk for anaphylaxis than those with reactivity only to the major determinant.[44] Conversely, skin testing can identify patients with histories of penicillin allergy who are at low risk (1–4%) for acute allergic reactions from a full course of penicillin therapy.[1,30,72] Skin testing is recommended in consultation with an allergist to confirm the risk of an acute reaction prior to treating the woman with a history of penicillin allergy (see Table 3).

Penicillin Desensitization

Recently at Parkland Memorial Hospital, the efficacy and safety of oral penicillin desensitization was investigated for pregnant women who had serious maternal–fetal infections (syphilis, endocarditis, listeriosis) best treated with a penicillin.[80] Fifteen women underwent a protocol using gradually increasing doses of oral phenoxymethylpen-

Table 4. *Oral Penicillin Desensitization Protocol*

DOSE	PHENOXYMETHYL PENICILLIN SUSPENSION	CUMULATIVE UNITS	DOSE
1	1,000 u/ml	100	100
2	"	200	300
3	"	400	700
4	"	800	1,500
5	"	1,600	3,100
6	"	3,200	6,300
7	"	6,400	12,700
8	10,000 u/ml	12,000	24,700
9	"	24,000	48,700
10	"	48,000	96,700
11	80,000 u/ml	80,000	176,700
12	"	160,000	336,700
13	"	320,000	656,700
14	"	640,000	1,296,700

Observe for 30 minutes
prior to administration of penicillin.

Interval between doses—15 minutes.
Phenoxymethyl penicillin suspension 250 mg/5 ml equals 80,000 units/ml.

icillin penicillin (Table 4) making them temporarily tolerant to a course of parenteral penicillin therapy. The desensitization was performed as an inpatient with intravenous access in place and resuscitation medications/equipment available. Although the procedure takes approximately 4 hours, patients are observed for 24 hours for delayed allergic reactions prior to discharge. Five of the fifteen patients experienced an allergic reaction during the protocol or after therapy, but all reactions were mild in nature. This is in accord with other studies of adults undergoing a similar oral desensitization protocol followed by penicillin therapy. Approximately 33 per cent of patients in these series experienced mild cutaneous reactions, and none experienced serious reactions.[70,73] The thirteen women with syphilis were adequately treated with appropriate doses of benzathine penicillin and congenital infection was prevented in all their infants.

COMPLICATIONS OF TREATMENT

Jarisch-Herxheimer Reaction

Because most women with syphilis will be treated during the early latent, secondary or primary stages, the incidence of Jarisch-Herxheimer reactions will be high.[4] In the nonpregnant adult, this reaction consists of fever, myalgias, headache, vasodilation, mild hypotension, and tachycardia.

Preliminary studies at our institution indicate that the Jarisch-Herxheimer in pregnant women also can include uterine contrac-

tions.[15] Fourteen of eighteen (78 per cent) women hospitalized at Parkland Memorial Hospital for treatment of primary or secondary syphilis in the second or third trimester have experienced Herxheimer reactions. Regular uterine contractions occurred almost synchronously with maternal fever in eleven (79 per cent) of those women. Fetal monitoring was performed, and some fetuses had transient evidence of fetal stress, as demonstrated by fetal tachycardia and decelerations occurring with uterine contractions. The women also reported a marked decrease in fetal activity for up to 24 hours after therapy. These changes were not present prior to the therapy nor were they demonstrable 24 hours after completion of therapy.

The etiology of the Jarisch-Herxheimer reaction is unknown, but prostaglandins may mediate the maternal cardiovascular changes and uterine activity noted.[15] It is not known whether premedication or treatment with antipyretics, antiprostaglandins, or steroids will ameliorate or protect the gravida or fetus from these problems. It is reasonable to treat fever with acetaminophen. Patients should be advised to report for evaluation any decreased fetal activity or uterine contractions that occur in the first 24 hours after treatment. Further research is needed into the role of the Jarisch-Herxheimer reaction and fetal stress after maternal therapy.

Treatment Failures

It has been noted that some women treated in the late second or third trimester of pregnancy will deliver premature affected infants or have a fetal demise soon after therapy.[4,15,49,77] Such treatment failures as well as those reported by the CDC raises questions about the efficacy of maternal penicillin therapy.[11] It is not known whether all the infants except the stillbirths had active congenital infection or resolving abnormalities from treated fetal infection. Benzathine penicillin may prevent congenital syphilis, if the fetal infection is incubating or mild at the time of treatment, but may not be able to eradicate or halt severe fetal disease. In a subgroup of fetuses already affected *in utero*, maternal treatment and its sequelae, particularly the Jarisch-Herxheimer reaction, may involve enough stress to result in premature labor or stillbirth. If this group could be accurately identified by sonography, alternate treatment regimens or medications to block the Jarisch-Herxheimer reaction could be tested. Treatment of the mother whose fetus may have severe fetal syphilis (i.e., markedly thickened placenta, hydramnios, hydrops, and ascites) is at high risk for failure. Consideration should be given to delivery and neonatal treatment if the fetus is near term.

NEONATAL TREATMENT

In the absence of a true "gold standard" for the diagnosis of congenital syphilis, infection often must be assumed and treatment with aqueous penicillin G administered (Table 5).[7,9] Some clinicians rec-

Table 5. *Recommendations for Treatment of Symptomatic or Asymptomatic Infants*

Aqueous crystalline penicillin G, 50,000 units/kg IM or IV daily in two divided doses for at least 10 days
or
Aqueous procaine penicillin G, 50,000 units/kg IM daily for at least 10 days

ommend treatment with a single injection of benzathine penicillin G, but this preparation is inadequate for treatment of congenital neurosyphilis.[7,51] Accordingly, when CNS system infection can not be definitely excluded, penicillin G is administered parenterally for a minimum of 10 days.[9,75] Although long-term sequelae of congenital neurosyphilis are incompletely understood, some treated infants will have normal developmental, neurologic, or behavioral function.

In general, infants should be treated if maternal therapy was inadequate, unknown, or late in gestation; did not include penicillin; or if followup of the infant is unlikely. Asymptomatic infants whose mothers were treated adequately during pregnancy do not need treatment unless followup cannot be assured. Infants whose mothers are unlikely to return for further examinations should receive a single dose of benzathine penicillin 50,000 units per kg intramuscularly.[9]

FOLLOWUP AND RETREATMENT

During Pregnancy

The gravida with syphilis requires attentive prenatal care, as she is often at risk for other complications of pregnancy due to other factors (e.g., her socioeconomic status). Monthly quantitative serologies are obtained until delivery to monitor response to therapy and rule out latent reinfection.[9] Patients should have a fourfold decrease in titer over 3 months with early syphilis,[6] but studies to support this trend in pregnant women are lacking. Women who develop a clinical recurrence, fail to show a fourfold decrease in titer in 3 months, or show a persistent fourfold increase in titer should be retreated. Patients who have high titers that do not respond to recommended regimens for early syphilis should have a lumbar puncture for CSF evaluation and be offered counseling and testing for HIV infection. Unless clinical manifestations indicate a reinfection, retreatment schedules should be for disease of greater than 1 year's duration (see Table 2).[9]

There are no published reports of seroresponse to therapy in pregnancy, but anecdotally it is not uncommon to see slow decreases in titer after treatment in pregnancy or slight increases in titers in serofast or seronegative women with adequate prior therapy.[41] As delays or omissions of treatment for reinfection can lead to congenital infec-

tion, at Parkland Memorial Hospital treatment is repeated in any pregnant woman with a history of prepregnancy therapy who has a VDRL titer greater than 1:2.

Postpartum

After delivery, serologic titers should be repeated at the same intervals as the CDC recommendations for adults.[9] Women with early syphilis should have postpartum followup to complete quantitative titer examination at 3, 6, and 12 months after therapy. A repeat serology is recommended 24 months after treatment for women with disease of unknown or more than 1 year's duration.

Sexual Partners

Current and recent sexual partners should be evaluated for clinical and serologic signs of syphilis. Treatment appropriate for their stage of infection is indicated. Those partners who are seronegative should be treated for possible incubating infections with the regimen for early syphilis (Table 2).[9]

Infants

Infected infants should receive at least the same follow-up examinations as normal newborns.[9,75] Quantitative serologies can be performed until they revert to negative at the 1-, 2-, 4-, 6-, and 12-month visits. Passively acquired maternal antibody from a serofast mother usually is gone by 3 months of age; persistent antibody after this period may indicate infection needing treatment. Children whose mothers were adequately treated in pregnancy can take up to 6 months to develop negative serologies. Infants with clinical infection treated in the neonatal period may take longer to revert to seronegativity but should have a nonreactive VDRL in peripheral blood by 9 months and CSF by 6 months. A lumbar puncture should be repeated at 6 months of age and compared to the neonatal CSF examination; if the VDRL is reactive the child needs to be retreated.[9,75]

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Management of Tuberculosis in Pregnancy and the Newborn

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Tuberculosis is a relatively uncommon infection for both pregnant women and the general population of the USA at the present time. Congenital tuberculosis is rare compared to the overall incidence of tuberculous disease in all children with most of the literature cited as single case reports. However, the severity of tuberculous disease, relatively high frequency of dissemination and death make the recognition, diagnosis and early treatment of infants extremely important.[17,23,30,31] The prevention of tuberculous infection in the fetus or the neonate requires a high index of suspicion, careful supervision, good judgment, and knowledge of the pathogenesis and clinical manifestations of this infection. The purpose of this article is to review the pathogenesis, clinical manifestations, diagnosis, treatment, and prevention of tuberculosis in pregnancy and the neonate.

The most recent statistics for tuberculosis among children were recently reported for 1985.[19] There were 1261 tuberculosis cases reported in children ages 0 to 14 years which represented a 2 per cent increase over the total for 1984. Of these patients, 47.4 per cent were white, 36.2 per cent black, 3.7 per cent Indian/Alaskan, and 12.7 per cent Asian–Pacific Islander. Of those children classified as white, 58 per cent (or 27.3 per cent of the total) were Hispanic. The importance of these numbers is reflected by the fact that: (1) these racial/ethnic groups continue to comprise the major groups of tuberculosis patients in the United States; (2) these groups continue to have the highest per capita birth rates in the United States; and, (3) we should therefore expect continuing or increasing numbers of cases of tuberculosis in pregnancy and congenital/neonatal infections.[8]

In congenital or childhood tuberculosis, there is no difference in incidence between the sexes. Poor living conditions, crowded hous-

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ing, and poor nutrition have always been associated with high tuberculosis rates.[35] The mortality from tuberculosis has declined more rapidly than morbidity in the United States. In 1976, Hinman et al. examined the changing risks for birth cohorts and demonstrated that the risk of dying from tuberculosis is now greatest for those below the age of 5 years.[22] This increased risk of mortality and difficulty in clinical diagnosis places the burden for the prevention of tuberculosis in pregnancy on health care workers.

PATHOGENESIS

Maternal

Hypotheses in regard to a relationship between pregnancy and host susceptibility to tuberculosis have provided vastly varying opinions. In the prechemotherapy era, there was much controversy as to the effect of pregnancy, delivery, or lactation on the course of tuberculosis in women. Medical opinion from Hippocrates and Galen down through 1835 held that these conditions had a beneficial effect. Then, beginning in the mid-19th century, the opposite view emerged, contending that pregnancy had a serious deleterious effect on the course of tuberculosis. Many authorities even advocated therapeutic abortion of any pregnancy occurring in a tuberculous woman.[45] However, more comprehensive studies, reported at the dawn of the chemotherapeutic era[9,13,20] indicated that there was no increased risk of progression of tuberculosis in either pregnancy or in the postpartum period, compared to nonpregnant women of the same age. The whole controversy has lost its importance since the development of effective chemotherapy for tuberculosis, which is as curative for pregnant or postpartum women as for the rest of the population.[2]

Currently, most investigators in published reports[11,37,38] do not feel that pregnancy is a factor predisposing to the development of tuberculosis. The mode of transmission of tubercle bacilli in pregnant women is consistent with transmission in all adults in which the organism is usually inhaled.[2] Pulmonary tuberculosis and asymptomatic Purified Protein Derivative (PPD) skin test conversions are the most common manifestations. However, lymphohematogenous spread or smoldering endometritis during pregnancy are particularly important in spread of organisms to the fetus or newborn at the time of delivery.[15,42] Untreated mothers with smear-positive pulmonary disease are a major route of transmission to the newborn and infant because of close physical contact in the postpartum period.

Fetus and Newborn

Tuberculosis in the fetus and newborn can be acquired in several ways: (1) hematogenously from the infected placenta via the umbilical vein, (2) aspiration of infected amniotic fluid *in utero*, (3) aspiration of infected material at the time of birth, (4) acquisition of infected

material from the mother or attendant during the neonatal period by inhalation, ingestion, or contamination of traumatized skin or mucous membranes.[15,23] Transmission of tuberculous infection to the fetus or newborn via the placenta or amniotic fluid has been reported in approximately 200 patients.[42] Tubercle bacilli have been found in placental specimens, tissue from stillborn infants, and living infants within a few days of birth.[39]

The liver is a major site of involvement in congenital tuberculosis.[4,17] Seeding from the umbilical vein, hepatic involvement with lymph nodes from the porta hepatis or mesentery is a common pathologic finding. In other patients (fetus or newborns), the lungs may be primarily involved, usually via direct transplacental transport by the ductus venosus branch of the umbilical vein or aspiration of infected amniotic fluid. A lower incidence of fetal involvement of the lungs compared to the liver also may be due to the lower oxygen content of fetal blood and hypoaeration of the lungs. With aeration and oxygenation of the lungs after birth, the persistence and replication of tubercle bacilli would be favored over primary hepatic involvement.[23]

The pathologic description of tuberculosis in the fetus and newborn demonstrates the predisposition to dissemination and fatal disease. The liver and lungs are the primary organs of involvement, with bone marrow, bone, gastrointestinal tract, adrenal glands, spleen, kidney, abdominal lymph nodes, and skin also being involved.[39] In congenital tuberculosis, the liver will have caseation with similar changes in adjacent abdominal lymph nodes. If the lungs are involved, mediastinal nodes are usually caseous with single or multiple parenchymal lesions. In some patients both organs may demonstrate these changes.[17,39] With hepatic involvement, the diagnosis of intrauterine acquisition is confirmed; however, if single or multiple pulmonary lesions are the only pathology present then several modes of transmission during or after delivery are possible and the diagnosis of congenital tuberculosis is not confirmed. Early reports[39] and Hageman, who reviewed congenital tuberculosis in the isoniazid (INH) era, noted that central nervous system (CNS) involvement was uncommon.[17]

Congenital and neonatally acquired tuberculosis, although rare, carries a mortality close to 50 per cent due primarily to the failure of clinicians to suspect the diagnosis of tuberculosis. Most fatal cases are diagnosed at autopsy.[17,31] On the other hand, if the diagnosis is suspected before the infant is moribund and appropriate treatment started, the prognosis for recovery is excellent.

The immunologic competence of the fetus and newborn regarding antimicrobial activity has been shown to be an important factor in their susceptibility to a number of infections.[52] Although the possibilities of inoculum size and repetitive exposures (close intimate contact with infected caretakers) may be a reason for this predisposition at a young age, several disease states (diabetes mellitus) and infections (measles and influenza) that affect the immune response in children and

adults[6,48,54] have demonstrated the importance of cell-mediated immunity in tuberculosis. Several investigators have speculated or demonstrated the importance of macrophage function against intracellular pathogens like *Mycobacterium tuberculosis*.[26,27] The activation of tissue macrophages by soluble mediators (cytokines), released on antigenic exposure of lymphoid and mononuclear cells, stimulate the macrophage and enhance its ability to ingest and kill increased numbers of organisms. A recent review summarized the differences between fetal/newborn and adult cytokine production and macrophage function.[52] This provides a possible explanation for the susceptibility to infection and predilection to a poor outcome in the fetus and newborn.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Maternal

A realization of the importance of clinical manifestations in pregnant women with tuberculosis must begin with the realization that as in all adults, asymptomatic disease occurs. Schaefer stated in 1975 that most patients whose tuberculosis is first discovered during pregnancy will be found to have inactive disease. In his series, tuberculosis was inactive in 88 per cent of cases.[38] Edge, reporting on cases collected in the 1940s, found that 72 per cent were inactive.[13] In those patients found to have active pulmonary tuberculosis at the New York Lying-In Hospital in the periods from 1933 to 1951, 1952 to 1972[38] and at Boston City Hospital in the 1940s,[9] their disease was classified as minimal in 60, 68, and 66 per cent and far advanced in 9, 11, and 14 per cent, respectively. This predominance of minimal disease probably accounts for the often-repeated statement that one half to two thirds of pregnant patients with tuberculosis are asymptomatic and unaware of their disease.[7,51] This is in contrast to a series of 6 pregnant and 21 postpartum patients (1–12 mo) reported from the National Jewish Hospital of Denver, in which only 19 percent were asymptomatic.[14] For the appropriate therapeutic course to be used, therefore, diagnosis must include history and epidemiologic investigation of case contacts and routine questioning of pregnant women in high-risk groups or from endemic areas.

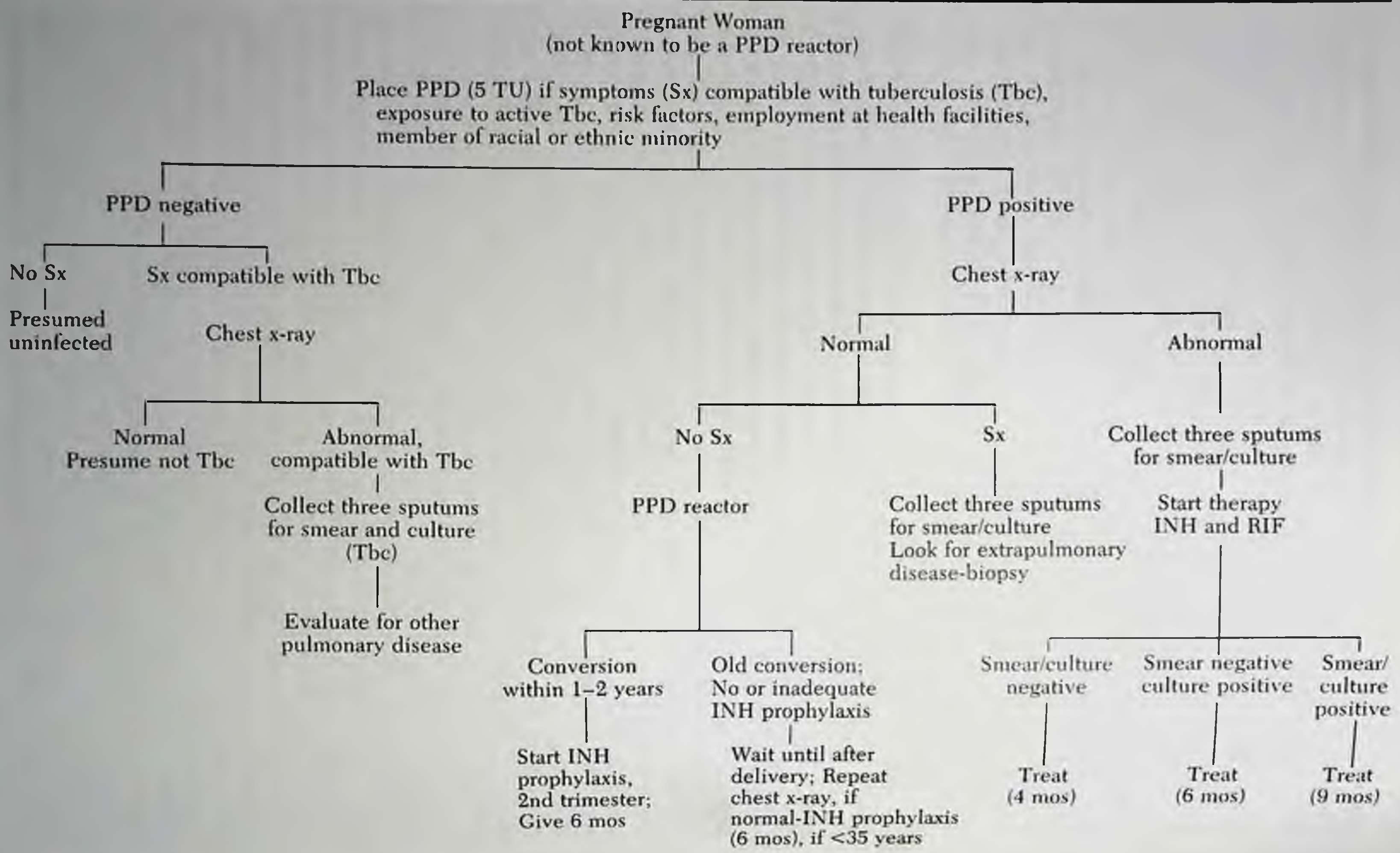
The most important screening method is tuberculin testing. Studies testing patients during and after pregnancy show no effect of pregnancy on the cutaneous tuberculin reaction.[33] Ideally, all pregnant women not known previously to be tuberculin reactors, should be skin tested. Given the difficulties of obtaining the 48 to 72 hour readings, however, it is probably more practical to test those patients: (1) with any sign or symptom suggestive of tuberculosis, (2) with a history of exposure to infectious subjects, (3) with risk factors such as diabetes or previous gastrectomy, or (4) employed in a hospital, nursing home, or prison. It is most important to skin test all women from the racial

and ethnic groups who are providing most of the tuberculosis seen in the United States today.[8] A careful history must be taken concerning the size of the reaction, the type of test applied, and the circumstances of the testing, when a patient states that she has had a previous positive tuberculin skin test result. If the history is not convincing, a PPD should be repeated. If the PPD reaction is positive, a chest roentgenogram (with shielding of the abdomen) must be obtained to determine if the patient has active disease. Sputum specimens for smear and culture should also be submitted. If there is evidence of extrapulmonary disease, appropriate biopsy specimens can be obtained for smears and cultures. If the patient has symptoms suggestive of tuberculosis, even if the PPD reaction is negative, chest roentgenograms, sputum specimens, and biopsies (if indicated) should be obtained. Skin testing of pregnant women in these groups and subsequent investigation of PPD reactors will allow the health care worker to properly approach the treatment of pregnant women (Table 1).

In a series of 27 pregnant and postpartum women with tuberculosis due to drug-sensitive (11 of 27) and resistant (16 of 27) organisms, Good et al. reported that cough (74 per cent), weight loss (41 per cent), fever (30 per cent), malaise and fatigue (30 per cent), and hemoptysis (19 per cent) were the most common clinical manifestations. Over 80 per cent of their patients were symptomatic. All patients in the drug-sensitive group (DS) and 15 out of 16 in the drug-resistant (DR) group had positive tuberculin skin tests. Chest roentgenograms were abnormal in all of their patients; patients in the DR group tended to have more extensive involvement of the lung. They also had a higher incidence of pulmonary complications, longer sputum conversion times and subsequent death.[14] Extrapulmonary involvement was uncommon in this series with only one patient manifesting genital tuberculosis at the time of presentation. In contrast, Selikoff and Dorfmann,[40] described 41 cases of extrapulmonary disease in 471 pregnant patients with diagnosed tuberculosis.

Tuberculous mastitis is a very rare entity that should be mentioned because it occurs almost exclusively in women of the childbearing years. In one series,[1] one third of the patients with tuberculous mastitis were lactating at the time of presentation. The most common finding was a single breast mass, with or without sinus drainage. Sinus drainage without an obvious mass or drainage from the nipple can also be seen. Nipple retraction and "peau d'orange" skin changes suggestive of carcinoma may be present. The axillary nodes usually are enlarged, either as individual or matted nodes. Only a minority of the patients have chest roentgenographic changes suggestive of current or old pulmonary tuberculosis. The PPD skin test result is usually positive but this is of minimal help in areas of endemic tuberculosis. The differential diagnosis is usually between a pyogenic breast abscess and carcinoma. A biopsy of the mass and an axillary lymph node should rule out carcinoma and demonstrate caseating granulomata. Smears and cultures of the tissue for *M. tuberculosis* are

Table 1. *Diagnosis and Treatment of Tuberculosis in the Pregnant Woman*



usually positive. Once a diagnostic biopsy has been obtained, treatment is usually successful with standard antituberculosis chemotherapy. Occasionally, a large residual mass may need to be resected. Mastectomy is never indicated unless there is coexisting carcinoma.[1,16,18,50]

The importance of diagnosis and intervention has been established by the recognition that untreated tuberculosis represents a far greater risk to a pregnant women and her fetus than does treatment of the disease.[43] However, tuberculosis during pregnancy is not an indication for a therapeutic abortion.[2,37] In 1975, Bjerekdal et al.[5] observed that women with active tuberculosis had a significantly higher incidence of spontaneous abortions and labor difficulties than did women in an uninfected group. This observation extended to women with a previous history of tuberculosis. Although they described a trend for an increased frequency of congenital malformations in children born to mothers with tuberculosis (2.9 per cent) compared to controls (2.2 per cent) the differences were not significant.[5] The importance of diagnosing tuberculosis in the pregnant woman is illustrated by these observations and emphasized by a review by Hageman et al.[17] in which 16 of 26 cases of neonatal tuberculosis were diagnosed prior to the diagnosis in the mother.

Fetus and Newborn

In 1935, Beitzke[4] established the criteria for the diagnosis of congenital tuberculosis: (1) *M. tuberculosis* must be present and proven; (2) the infant has a primary complex in the liver; (3) the lesions are present within the first days of life; or (4) if the infant has neither a proven hepatic primary nor lesions present in the first days of life, extrauterine infection must be excluded. Although the prevention of congenital tuberculosis by treatment of pregnant women and the diagnosis and early treatment of newborns is more important, this established definition is useful in confirming the mode of transmission and course of infection.

The clinical manifestations vary in relationship to the site and size of caseous lesions. Symptoms are usually present by the second or third week of life. The most common are respiratory distress, fever, and hepatosplenomegaly, which may cause abdominal distension. About half the patients have anorexia, poor weight gain, lethargy, or irritability. Peripheral lymphadenopathy is seen in approximately one third of cases. Ear drainage and skin lesions are sometimes noted.[10,17,30,36,42,47,49] In a single case reported where wasting was a major manifestation, hypoadrenocorticism was documented.[28]

Most patients present with an abnormal chest roentgenogram, about half of which show a miliary pattern. Other patients may develop roentgenographic abnormalities later during the course of their illness. The course may be that of a progressive primary tuberculosis with a steadily enlarging pulmonary infiltrate and a caseous center that may liquify and discharge, leaving a cavity.[17,42]

An acute febrile course may suggest bacterial sepsis, but the fever

and pulmonary abnormalities fail to respond to vigorous antibiotic therapy. This situation should always suggest the possibility of tuberculosis.

The potential spread of tuberculosis in the nursery has always been a concern to health care workers. Although the possibility exists especially from an infant with caseous pulmonary cavitary involvement, the documented risk is low. Myers et al. reported in 1981 on 107 exposed neonates in a nursery setting of which 65 infants were available for extended followup of several months.[30] They found no evidence of infection and all infants were skin test negative. All hospital personnel were also found to be free of infection.

The diagnosis of congenital or neonatal tuberculosis is difficult. The tuberculin test is nearly always negative initially, although it often becomes positive 6 weeks to 4 months later. Therefore, after tuberculosis is suspected, the diagnosis must be established by finding the acid-fast bacilli (AFB) in body fluids or in a biopsy and culturing *M. tuberculosis*. Properly done, early morning gastric aspirates are noninvasive and highly productive of positive cultures, which become available in a few weeks. Urine cultures are similarly noninvasive. Direct smears on gastric aspirates are not reliable. However, direct smears from middle ear fluid, bone marrow, or tracheal aspirates, or those from biopsies of skin lesions, peripheral lymph nodes, or lung may show AFB. An open liver biopsy should be a highly productive procedure for the diagnosis of tuberculosis in an infant and should be done more often. All specimens should be submitted for cultures and drug susceptibility studies. The cerebrospinal fluid should be examined and cultured, although the yield is usually very low.[17,42]

A high index of suspicion should be triggered if the mother is known to have had recent active tuberculous disease or if she develops an active lesion during the puerperium.[36] The history and epidemiology of a fetus or infant at risk is the most important diagnostic modality that health care workers can use for effective diagnosis and treatment of tuberculous disease in newborns and infants. If all direct smears prove negative and the infant is still ill, antituberculosis chemotherapy should be started empirically while results of cultures are pending.

TREATMENT

Maternal

The indications for treatment of active tuberculosis in a pregnant patient are the same as for other patients. Two drugs in standard doses must be used, and the duration of treatment is 9 months. The only question is the choice of drugs. Fortunately, there has been experience with the first line antituberculosis drugs in pregnancy.

The most extensive experience has been with isoniazid (INH) in over 1400 cases. Although INH crosses the placenta there seems to

be no teratogenic effect, even when given during the first 4 months of gestation. The next most frequently used drug has been ethambutol (EMB), 650 cases, with no evidence of fetal malformations including eye abnormalities. Rifampin (RIF) can cross the placenta and might cause fetal damage due to its ability to inhibit DNA-dependent RNA polymerases. However, 446 pregnancies exposed to RIF produced only 3 per cent abnormal fetuses, compared with 2 per cent with EMB and 1 per cent with INH. The abnormalities included limb reductions (3), central nervous system abnormalities (3) and hypoprothrombinemia (13). These are not significant numbers, however, because the incidence of abnormal fetuses in normal pregnancies ranges from 1.4 to 6 per cent.[43]

On the other hand, 206 pregnancies exposed to streptomycin (SM) produced 35 abnormal infants, all but one of which had eighth nerve damage, a 17 per cent defect rate. Abnormalities ranged from vestibular damage or mild hearing loss to severe bilateral deafness. The action of SM seems to be independent of the "critical periods" in embryogenesis and is potentially hazardous throughout pregnancy. It is assumed that capreomycin and kanamycin could have the same toxic potential as SM. Little is known about the effects of pyrazinamide (PZA) in pregnancy. Teratogenic effects have been attributed to ethionamide. Cycloserine should be avoided because of its CNS side effects.[43]

The recommended treatment of active tuberculosis in pregnancy is with INH and RIF daily, initially, with the addition of EMB, 25 mg per kg (bactericidal dose), if there is the possibility of INH resistance. Pyridoxine, 50 mg daily, should always be given with INH during pregnancy because of the increased requirements for this vitamin in pregnant women.[44] When drug susceptibilities are available and the organism is found to be sensitive to all drugs, treatment after the first 1 to 2 months may be given twice weekly. EMB may also be given twice weekly (see Table 2 for drug doses, daily and twice weekly). Since PZA is not used, the duration of therapy must be 9 months.

If the mother is infected with a multidrug-resistant organism, some of the unknown or contraindicated medications may be required for adequate treatment of her tuberculosis. Under these circumstances and because of the possible serious effect on the fetus, therapeutic abortion might need to be considered.[14]

Treatment of tuberculosis in pregnant women often will continue after delivery. The question then arises as to whether it is safe for the mother to breastfeed her infant. Snider and Powell have addressed this issue[46] and concluded that the infant would receive less than 20 per cent of the INH ingested and less than 11 per cent of other antituberculosis drugs. This should not be enough to cause symptoms. It is also not sufficient for the treatment of tuberculosis. If the infant is also receiving antituberculosis therapy, the additional medication from the breast milk might add to the toxicity, and therefore breastfeeding probably should be discontinued in that instance.

Table 2. *Treatment of Tuberculosis in Adults and Children*

DRUG	DOSAGE				ADVERSE REACTIONS AND COMMENTS
	Dosage forms	*Daily dose*	*Twice weekly dosage*	*Maximum daily dosage*	
Isoniazid	Tablets: 100 mg 300 mg Syrup: 50 mg/5 ml Vials: 1 gm	10 to 20 mg/kg/day	20 to 40 mg/kg	300 mg/day maximum; twice weekly: 900 mg maximum	Mild hepatic enzyme elevation, peripheral neuritis, hepatitis, hypersensitivity
Rifampin	Capsules: 150 mg 300 mg Syrup: formulated from capsules, 10 mg/ml	10 to 20 mg/kg/day	10 to 20 mg/kg	600 mg	Orange discoloration of secretions/urine; nausea, vomiting, hepatitis, febrile reaction, purpura (rare)
Pyrazinamide	Tablets: 500 mg	30 mg/kg/day	50 mg/kg	2 gm	Hepatotoxicity, hyperuricemia
Streptomycin	Vials: 1 gm, 4 gm	20 mg/kg/day IM, 5 days/wk	25 to 30 mg/kg	1 gm	Ototoxicity, nephrotoxicity
Ethambutol	Tablets: 100 mg 400 mg	15 to 25 mg/kg/day	50 mg/kg	2.5 gm	Optic neuritis (reversible): red-green color discrimination, visual activity, skin rash, not suitable for children unable to perform visual screening
		Less commonly used agents			
Capreomycin	Vials: 1 gm	20 mg/kg/day, im 5 days/week		1 gm	Ototoxicity, nephrotoxicity
Kanamycin	Vials: 500 mg/2 ml, 1 gm/3 ml, 75 mg/2 ml	15–30 mg/kg/day, IM		1 gm	Auditory toxicity, nephrotoxicity, vestibular toxicity
Ethionamide	Vials: 250 mg	15–20 mg/kg/day		1 gm	Gastrointestinal disturbance, hepatoxicity, hypersensitivity
Para-aminosalicylic acid	Tablets: 500 mg Resin packets: 4 gm	150 mg/kg/day		12 gm	Gastrointestinal disturbance, hepatotoxicity, hypersensitivity, sodium load
Cycloserine	Capsules: 250 mg	10–20 mg/kg/day		1 gm	Psychosis, personality changes, convulsions, rash

Treatment of Congenital or Neonatally Acquired Tuberculosis

Tuberculosis should be suspected in any neonate or infant with nonresponsive pulmonary disease. The treatment of congenital or neonatally acquired tuberculosis is the same as for older children. If the diagnosis of tuberculosis can be established or even suspected early enough, a complete response to treatment can be expected.

There is little specific information in the literature about treatment of congenital or neonatally acquired tuberculosis. Hageman reported 26 patients seen since the introduction of INH in 1952. There were 12 deaths, a mortality of 46 per cent. However, in nine instances, the diagnosis was made at autopsy, and therefore the patients were not treated. Two were treated only 1 and 5 days respectively. A final patient received INH, para-aminosalicyclic acid (PAS) and SM for 14 days before death.[17] Nemir collected an additional 14 patients in 1985. There were seven deaths, a mortality of 50 per cent. Six were diagnosed at autopsy and the last died at 46 days, after only 2 days of treatment.[31] Recently, three additional cases have been reported, two survived, and one died.[3,10,29]

Analysis of seven cases reported in detail regarding diagnosis, treatment, and course suggests that the prognosis is worse for the premature infant.[3,10,17,29,30,47] An 880 gram female, born after 28 weeks' gestation received no treatment until 44 days of age, 7 days after the diagnosis of tuberculosis was made in her mother. She died 2 days later.[30] A 1380-gm male, 28 weeks' gestation, was diagnosed at 28 days when AFB were seen in a tracheal aspirate, but died 3 weeks later despite treatment with unspecified amounts of INH, RIF, and SM.[3] Three surviving infants had birth weights of 3.0, 3.0, and 3.8 kg and a fourth was delivered after a 36-week gestation. The fifth was a 1660-gm female, product of a 30-week gestation.[10,17,29,47]

Information on drugs and doses is also scanty. Voyce and Hunt reported an 8-week-old infant who died after 2 weeks of INH, para-aminosalicylic acid (PAS), and SM treatment. His mother had received 2 years of INH, PAS, and SM, concluding at the fifth month of her pregnancy.[49] Hageman reported the death of an infant treated for 2 weeks with INH, PAS, and SM. These studies suggest that this formerly standard regimen was not always adequate.[17] All of the surviving cases received both INH and RIF. Doses of INH ranged from 12 to 20 mg per kg and RIF doses from 10 to 15 mg per kg. One patient also received EMB, 15 mg per kg and another was given prednisone 2 mg per kg. Only 3 infants were given SM with one survivor.

Once a reasonable suspicion of tuberculosis has been established in a neonate or infant and appropriate biopsies and body fluids obtained for histologic examination, smears and cultures, treatment should begin with INH and RIF daily. If there is any possibility that the infection may be with drug-resistant organisms, initial treatment with 4 drugs is recommended. Streptomycin appears to be effective and safe in young children. Both PZA and EMB have been used in children as young as 1 year of age with tuberculous meningitis and

spinal tuberculosis without serious side effects.[3,4] We usually prefer INH, RIF, SM, and PZA for cases of possible drug resistance and try to avoid EMB in young children because of the possibility of retrobulbar neuritis and the inability to check visual acuity in the infant. Once drug susceptibility results are available on the organism of the patient or his source case, treatment can continue twice weekly with two bactericidal drugs. If PZA, INH, and RIF are given daily for the first 2 months, a total of 6 months treatment is adequate. Otherwise, the treatment should be for 9 months. All first-line bactericidal drugs should be administered once daily. The reproduction time of the tubercle bacillus is 14 to 22 hours.[41] Pediatric doses for daily and twice weekly therapy are shown in Table 2.

Preventive Treatment During Pregnancy

If a pregnant woman is found to be PPD positive and active disease has been ruled out, INH prophylaxis will be needed at some time. It is recommended that INH be started immediately postpartum if the chest roentgenogram is still normal at that time. If the PPD conversion occurred within the previous 1 to 2 years, INH prophylaxis should be started during the second trimester of the pregnancy.

Management of the Infant of a Tuberculous Mother

If the mother has completed a course of antituberculosis therapy in the past, there is minimal risk to her newborn. If the mother is on antituberculosis chemotherapy during pregnancy and her sputum culture has converted to negative, there should be minimal risk to the newborn. The infant should be skin tested at birth and at 3-month intervals. If the mother has been treated for a shorter length of time, the infant should be investigated thoroughly for tuberculous infection. If no evidence of disease is found, INH prophylaxis is initiated in the infant provided the mother's organisms are susceptible to INH. Daily INH can protect the newborn against acquiring tuberculosis.[12] If the family cannot be relied on to give the INH or if other household members are suspected of being infected, BCG can be considered for the newborn infant.

The infants of mothers with active tuberculosis at the time of delivery were studied by Kendig in 1969. Thirty infants received BCG vaccinations at birth and 24 of these were also isolated from their mothers for up to 6 weeks; none developed tuberculosis. In contrast, 38 cases of tuberculosis and three deaths occurred in 75 infants who remained with their mothers and received no INH prophylaxis.[24] At the present time, few people believe that BCG vaccine is sufficiently effective and the general opinion is that BCG has no place in the management of tuberculosis in developed countries. However, recent articles suggest a significant decrease in overall incidence of tuberculosis in children vaccinated with BCG at birth and some decrease in the severity of the disease when it occurs. In a study of child contacts of active cases of tuberculosis in Thailand, the incidence of tuberculosis in BCG vaccinated children, 81 per cent of the total, was

13 per cent compared with 24 per cent in nonvaccinated children. Culture-proven tuberculosis occurred in 4 per cent of the vaccinated and 8 per cent of the unvaccinated.[32] A case-controlled study in Canadian Indian and Eskimo children, for whom newborn BCG vaccination has been recommended since the 1960s, showed a 60 per cent protective effect of vaccination against tuberculosis.[53]

BCG vaccination of the newborn appears to be safe, easy to administer, and requires no cooperation from the family. It does appear to have some protective effect against the development of tuberculosis and probably some decrease in the serious forms of the disease. Because BCG promotes the development of tuberculin sensitivity, it could theoretically interfere with the use of the PPD skin test as a case-finding device. Lipschitz has shown that not only does the reactivity from BCG largely disappear within 1 year of vaccination but also that children with PPD reactions of 10 mm or more could be easily identified as infected with *M. tuberculosis*.[25] BCG might be considered for a newborn who would be living in a chaotic home situation where the risk of tuberculosis infection is high.

In summary, the diagnosis of tuberculosis in the pregnant woman and the prompt institution of chemotherapy are the most effective means of preventing serious disease in the newborn and infant.

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Perinatal Infections with *Chlamydia Trachomatis*

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> It can be stated with certainty that the virus of inclusion conjunctivitis is one of the causes of nongonococcic urethritis . . . that the localization of the virus in the female is in the cervix in the transitional epithelium just within the external os . . . [and] that the disease produced by the virus in the female is in most instances subclinical.
>
> THYGESON AND STONE, 1942[121]

Most of the basic epidemiology of perinatal infection with *Chlamydia trachomatis* was described decades before the isolation, propagation, and microbiologic characterization of the organism were accomplished. Within several years of the first description of intracytoplasmic inclusions in conjunctival scrapings from trachoma patients by Halberstaedter and von Prowazek (1907), Lindner and coworkers had described identical inclusion bodies in nongonococcal neonatal eye infections. Between 1909 and 1911, these workers convincingly demonstrated that the agent of "inclusion blennorrhea" was transmissible to primates and could be demonstrated cytologically in urethral and cervical smears from affected infants' mothers and in urethral smears from these women's sexual partners. During the 1930s, elegant epidemiologic studies by Thygeson and colleagues highlighted the importance of venereal transmission of this filtratable agent in producing perinatal disease.[121] The likelihoods that most maternal infections were asymptomatic and that postpartum fever and genital discharge might be associated with such infection were both appreciated. The possibility that *Chlamydia trachomatis* infection of nonpregnant women might be related to pelvic inflammatory disease was raised.[121] Many of the initial studies of perinatal chlamydial in-

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fection since the mid-1970s only rediscovered these long-described associations.

However, important advances have been made during the past decade in several areas relating to *C. trachomatis* as a perinatal pathogen. Afebrile pneumonia in a young infant due to *C. trachomatis* was first described in 1975.[112] A series of increasingly comprehensive and sophisticated microbiologic and epidemiologic studies has begun to define the contribution of this organism to adverse pregnancy outcome. Applications of techniques in molecular biology, such as monoclonal antibody production and gene cloning, have facilitated development of rapid diagnostic techniques and promise to provide new insights into the pathogenesis and the immunology of chlamydial infection.

This review summarizes the relevant microbiology of chlamydiae, highlights the clinical and epidemiologic features of perinatal and neonatal infections, and outlines current diagnostic and therapeutic approaches to these infections.

MICROBIOLOGY

Long classified as "viruses" because of their ability to pass through 0.4 μ filters and because of obligate intracellular parasitism, chlamydiae are now known to be highly specialized gram-negative bacteria.[127] They possess a trilaminar cell wall similar to gram-negative bacilli and produce a genus-specific, heat-stable glycolipid outer cell wall antigen. This moiety is very similar to the lipid A—2-keto-3-deoxyoctonoic acid core lipopolysaccharide or endotoxin of Enterobacteriaceae, and cross reacts with "core LPS" of mutant Salmonella strains and Acinetobacter.[85] Serologic tests that detect antibody against this genus-specific complement-fixing antigen may therefore not be chlamydia specific. The cell wall does not contain conventional peptidoglycans, muramic acid, or penicillin-binding proteins. These findings provide partial explanation for the lack of in vitro activity of most penicillins and all cephalosporins against *C. trachomatis*.

Chlamydiae contain both DNA and RNA. The genome consists of approximately 8×10^5 nucleotide base pairs, much smaller than conventional bacteria and comparable in size to that of mycoplasmas. Sufficient genetic information is carried to code for several hundred different proteins. There is limited DNA homology among the species of *C. trachomatis*, *C. psittaci*, and the recently described TWAR strain. Within the species *C. trachomatis*, there is considerable DNA relatedness, even among strains associated with trachoma, genital infection, or lymphogranuloma venereum.[108, 127]

Chlamydiae are unable to synthesize high-energy phosphate compounds and are therefore "ATP-parasites," depending on host cells for generation of these vital metabolites. For this reason, cell-free cultivation of chlamydiae is impossible.

A unique biphasic life cycle has evolved that allows both a cell-

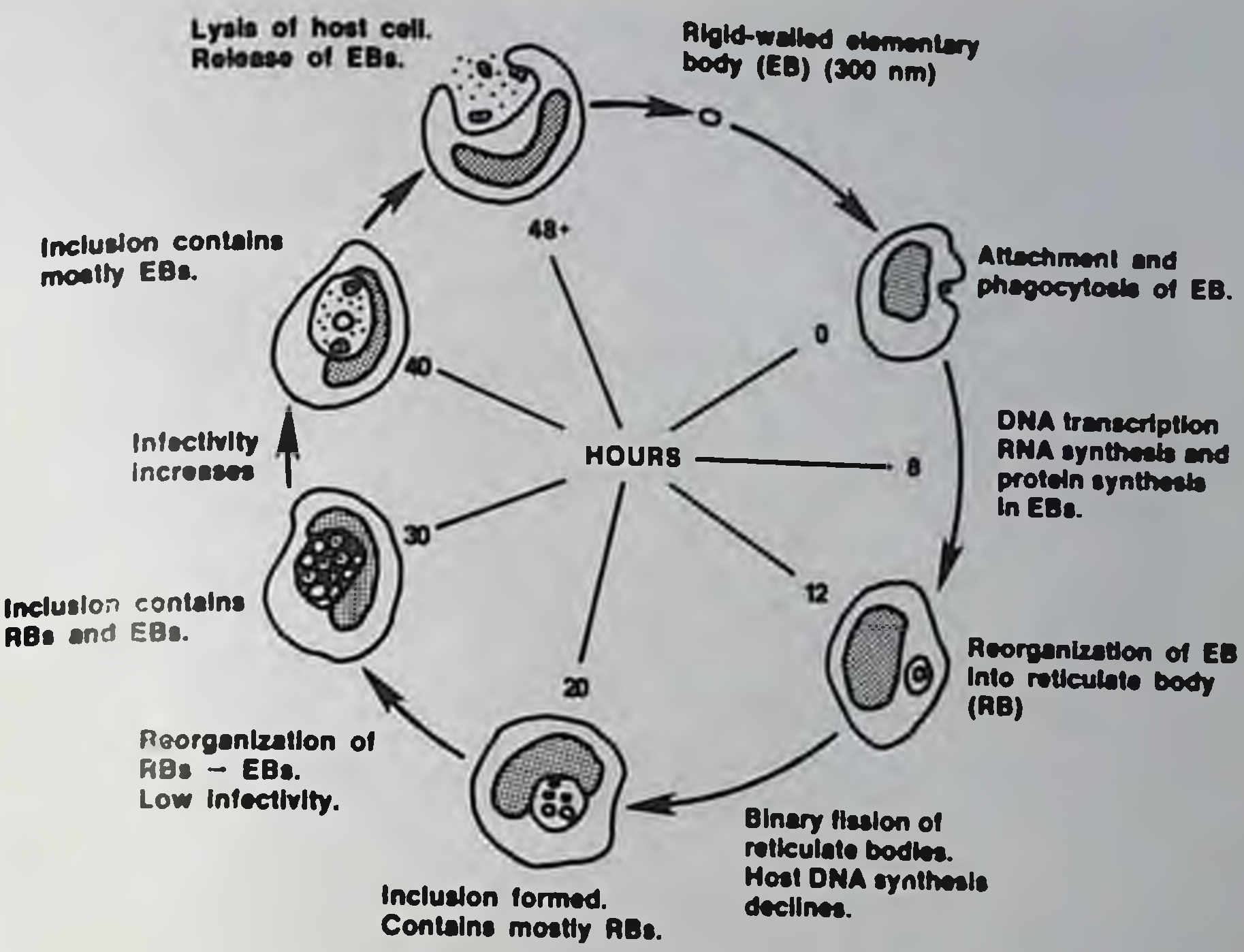

Figure 1. Diagrammatic representation of chlamydial replication cycle.

free, stable, extracellular infective form and an intracellular, metabolically active, replicating form (Fig. 1).[108, 127] The infectious form is the elementary body, a rigid, thick-walled, metabolically inactive form, approximately 350 nm in diameter. Elementary bodies have a cell wall rich in proteins, with many disulfide cross-links that may provide rigidity and protection in the extracellular environment. Elementary bodies attach to host cells and are taken up by nonprofessional phagocytes via endocytosis. This phagocytic vacuole becomes the inclusion body in which the organism will replicate intracellularly. This vesicle does not fuse with lysosomal membranes. (This specialized endocytosis and the lack of phagolysosomal fusion are properties unique to chlamydiae.) Within 6 to 8 hours of infection, elementary bodies (EB) enlarge and transform to reticulate bodies, 700 to 1000 nm in size. The cell envelope is less rigid and the DNA less compact. These forms synthesize mRNA and replicate by binary fission, using host cell ATP and certain amino acids. Maturing inclusions contain both elementary bodies and reticulate bodies (Fig. 2). Twenty hours after cell infection, reticulate bodies begin to reorganize and condense to form progeny elementary bodies. Large numbers of new, infectious EBs are released by cell lysis 24 to 36 hours after initiation of infection.

A number of antigens of *C. trachomatis* have been isolated and characterized.[1, 68] The major genus-specific antigen is the chlamydial LPS molecule. Species- and subspecies-specific membrane proteins

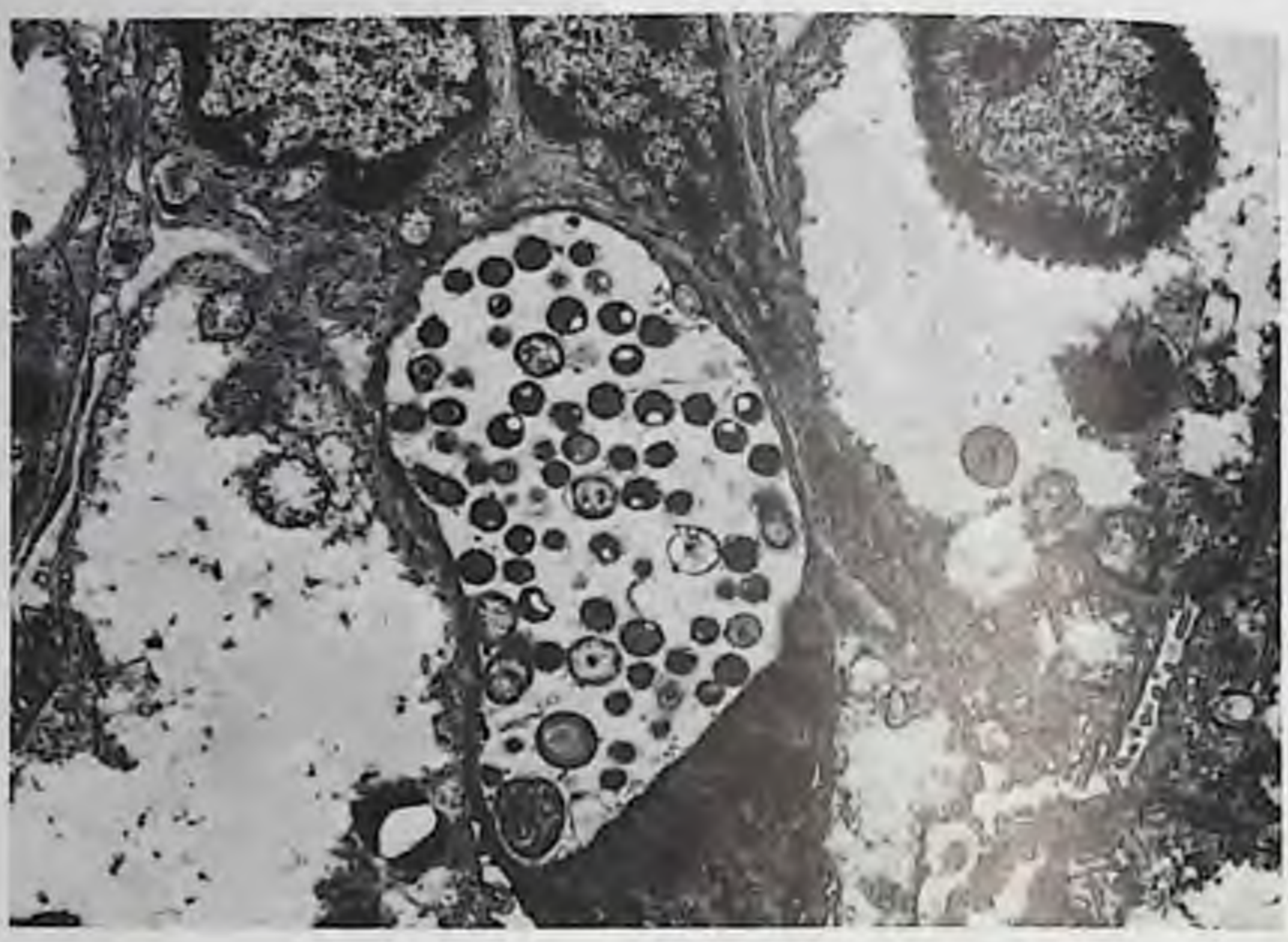

Figure 2. Electron photomicrograph of chlamydial inclusion body within alveolar lining cell of fetal rat lung. Note electron dense elementary bodies and larger initial and reticulate bodies. (Original magnification 5000 ×.)

range in molecular weight (MW) from 155,000 to 38,000. There is a species-specific antigen with MW of 60,000 to 62,000 Kd, which is a cysteine-rich doublet component of the outer membrane. The major outer membrane proteins (MOMP) range from 38,000 to 42,000 in MW and contain species- , subspecies- , and serovar-specific epitopes. Distinct serovar-specific proteins of MW 27,000 to 30,000 are associated with esterase activity and are heat and protease sensitive. The major biologic roles of these various proteins and of antibody responses elicited by these remain to be identified. Monoclonal antibodies to MOMP have been shown to neutralize infection in vitro, but in vivo correlates of this protection in human immunity are lacking.[89]

Non-LGV strains of *C. trachomatis* preferentially infect columnar epithelial cells. Infection is initiated by attachment of elementary bodies to the host cell surface, probably via specific receptors. The identity of these molecules and the mechanisms of subsequent endocytosis have not been elucidated. In vitro, either McCoy cells (a murine fibroblast line) or HeLa cells (strain 229) are most commonly used for isolation of *C. trachomatis*. Infection of cultured cells is facilitated by pretreatment of monolayers with cycloheximide or iodoxuridine and by centrifugation of the inoculum. This latter step may induce membrane changes in the cultured cell's surface, either exposing or rearranging binding sites, rather than merely physically deposit EBs. Infective inclusions may be detected by Giemsa stain, by fluorescent antibody stain (using monoclonal antibodies), or by staining with

Jones' iodine. The latter stains the glycogen-rich matrix within the inclusion vacuole of *C. trachomatis*. (Inclusions produced by *C. psittaci* are diffuse and do not contain glycogen and therefore do not stain within iodine.) Fluorescent staining of inclusions with monoclonal antibody, using cycloheximide-treated McCoy cells, is currently felt to be the most sensitive method for isolating *C. trachomatis*.

C. PSITTACI INFECTION AND PREGNANCY

Psittacosis, or ornithosis, is a pulmonary and systemic infection of humans due to infection with avian strains of *C. psittaci*. Infection is contracted from psittacine birds (parrots and related species) or from other species (turkeys, ducks, pigeons). There are few contemporary reports of the manifestations of psitticosis during pregnancy, possibly because most exposures to this infection are now occupational in veterinarians, poultry (duck and turkey) farmers, and poultry-processing workers. Pregnant women are probably at low risk of such exposures. Schachter quotes Vaag, citing an extremely high mortality rate in infected pregnant women in the Faroe Islands outbreak of 1938; 11 of 14 pregnant women with psittacosis died.[109]

Nonavian chlamydiae rarely infect humans. However, Roberts et al. in 1967 reported human abortion due to infection of a 22-year-old woman with the chlamydial agent of ovine abortion.[103] This strain causes intense placental inflammation with villitis and is an important enzootic cause of abortion in sheep. More recently, Johnson and Wong[62, 76, 129] have reported three women who were 25 to 28 weeks pregnant and had contact with infected sheep during the lambing season. Severe clinical illnesses with renal failure and disseminated coagulation developed in all these patients; two infants were stillborn and the third died at 2 hours of age. Pathologic examinations of the placentas revealed intense inflammation in the intervillous spaces and chlamydial inclusions within trophoblastic cells.[129] In another similar case, both mother and fetus succumbed.[9] Based on these few cases with very poor fetal outcome, pregnant women should not have contact with sheep, particularly during the lambing season.

A new strain of *Chlamydiae*, named TWAR (for *T*ai*w*an and *a*cute *r*espiratory, designations given the first two isolates), recently has been associated with acute upper and lower respiratory infections.[44] This strain microbiologically is more similar to *C. psittaci* than to *C. trachomatis*, but appears to a genetically distinct species by DNA homology.[26] Respiratory disease may be manifest as pharyngitis, bronchitis, or pneumonia. The latter is similar to other "atypical pneumonias," with a prolonged clinical course marked by coughing. Infection appears to be most prevalent in young adults. No animal reservoir has been described, and transmission is assumed to be person to person. To date there have been no descriptions of the course of this infection during pregnancy, and no studies of its effects on the fetus or on pregnancy outcome.

CHLAMYDIA TRACHOMATIS INFECTION DURING PREGNANCY

Epidemiologic Features

A large number of studies have defined risk factors for chlamydial cervical infections of nonpregnant women[4, 24, 29, 35, 38, 41, 55, 64, 75, 105, 113, 115, 123]; many of these also apply to gravid women. The single most important determinant of infection in nonpregnant women is age; teenaged women have higher prevalence rates of cervical chlamydial infection than do women in their twenties.[38, 55, 113, 123] Teenagers less than 18 years of age are more likely to be infected than older adolescents. Black women are more likely to be chlamydia-positive than are white women in most studies,[35, 75, 113, 115] but not in all.[4, 24, 38, 41] Oral contraceptive use correlates with chlamydial cervical colonization in many studies,[4, 38, 55, 64, 75, 113, 115] although not in all studies.[24, 29, 35, 41] The reasons for this increased infection rate are unclear. Ectopy is more prominent in women using hormonal contraceptives and may increase the likelihood of cervical infection[4, 29, 55, 75] but is also age related. Use of barrier contraceptives may be protective,[55, 75] but the relationship to oral contraceptive use is not based on lack of barrier methods alone. Hormonal changes enhance chlamydial genital infection in experimental animals,[87, 125] but the roles of estrogen and progesterone in human infection are undefined. From 32 to 68 per cent of nonpregnant women with chlamydial cervical infection are asymptomatic. Prevalence rates are higher in women being seen in STD clinics or adolescent clinics than in private gynecologists' offices or family planning centers. Prior STDs, especially gonorrhea, are risk factors.[17, 29, 41] (From 25 to 42 per cent of women with gonorrhea have concurrent chlamydial infection.) Physical and laboratory findings associated with chlamydial cervicitis include ectopy, cervical erythema and friability, or endocervical discharge,[4, 22, 29, 35, 55, 73, 113, 123] increased polymorphonuclear leukocytes in vaginal or cervical secretions,[24, 55, 80] and increased inflammatory cells on Pap smear.[24, 115] Behavioral correlates in many studies include early age at first sexual intercourse, increased number of sexual partners, and having partners with urethritis or other STDs.

Pregnancy may itself increase the risk of being colonized with *C. trachomatis*. This possibility is suggested by several studies, particularly in adolescents, in which pregnant subjects had higher prevalence rates than nonpregnant women in the same population (Table 1). The epidemiologic or biologic reasons for these higher prevalences in pregnant adolescents have not been defined.

Infection rates during pregnancy vary widely, from 2.0 to 47 per cent.[12, 13, 29, 30, 35, 41, 43, 47, 53, 54, 59, 60, 69, 71, 72, 83, 90, 111, 116, 119, 120, 123] Low rates have been reported from Boston (1.9 per cent),[47] Malmo, Sweden (2.4 per cent),[90] San Francisco (4.7 per cent),[111] Norway (5.8 per cent),[116] and Seattle (6.7 per cent).[71] Prevalences differ by the type of patient population studied, with factors such as racial and so-

Table 1. *Prevalences of Chlamydial Infection in Pregnant versus Nonpregnant Women*

STUDY LOCATION	AGE OF WOMEN (YEARS)	CHLAMYDIAL PREVALENCES	
		Pregnant (%)	*Nonpregnant (%)*
Baltimore[29]	13–18	19/70 (27)	47/190 (23)
Brooklyn[41]	12–17	10/62 (16)	9/124 (7.2)
Denver[35]	12–18	23/86 (27)	62/310 (20)
Alaska[123]	"Teenagers"	7/15 (47)	24/65 (37)

cioeconomic backgrounds and previous exposures to sexually transmitted diseases being more important than geographic site. High prevalences have been reported from Cleveland (18 per cent),[59] Chicago (21 per cent),[60] New Mexico (22 per cent),[12] New Orleans (23 per cent),[72] Baltimore (37 per cent),[53] and Alaska (30 per cent).[123]

Age is the single most important determinant of chlamydial cervical colonization during pregnancy. As noted above, prevalences are highest in adolescents, ranging from 16 per cent in Brooklyn,[41] to 27 per cent in Baltimore[29] and Denver,[35] to 47 per cent in Alaska.[123] This inverse relationship to age is observed in both low-prevalence[90] and high-prevalence[120] populations. In a Swedish population with an overall prevalence of 2.4 per cent, 7.1 per cent of women ≤19 years of age, 3.7 per cent of 20- to 24-year-old patients, 2.3 per cent of 25- to 29-year-old patients, and 0.5 per cent of women 30 years or older had positive results.[90] In an Atlanta, Georgia, population with an overall prevalence of 16 per cent, 21.9 per cent of women 19 years old or less, 16.1 per cent of 20 to 24 year olds, and 10.5 per cent of women 25 years or older had positive results.[120] Whether these differences reflect eventual development of protective immunity, or are due to undefined biologic, epidemiologic, or behavioral characteristics of younger women, is unanswered.

Race may be an important risk factor; many studies,[54, 72] but not all,[119] report blacks as having higher prevalences than white women. High prevalences have also been reported in Navajo women (22 per cent)[12] and Alaskan Eskimos (30 per cent).[123] Higher prevalences also have been observed in women who are unmarried,[72] who have less than complete high school education,[12, 54] and who are from lower socioeconomic strata.[54] Multiple sexual partners[54, 72] and early age at first intercourse[54, 72] have correlated chlamydial cervical infection in some studies. Coinfection or previous infection with the gonococcus is a frequent risk factor.[12, 13, 72] Other sexually transmitted organisms, such as group B streptococcus[83] or trichomonas,[72] have been associated with chlamydial infection (Table 2).

Pregnant women colonized cervically with chlamydia are rarely symptomatic. Most infected women have no symptoms of discharge,

Table 2. *Risk Factors for Chlamydial Infection in Pregnancy*

RISK FACTOR	STUDY	A	B	C	D	E	F	G
Younger age		+	+	+	+	+	–	+
Black race		+	–	–	+	NT	–	–
Single marital status		+	–	–	–	–	–	+
Lower SEC		–	–	NT	+	NT	NT	+
Education ≤12th grade		–	–	NT	+	+	NT	NT
First intercourse at ≤17 years		+	–	NT	+	NT	NT	NT
≥3 Lifetime sexual partners		+	–	NT	+	NT	NT	NT
Prior gonorrhea		+	–	+	NT	+	NT	NT
Trichomoniasis during pregnancy		+	–	–	–	NT	NT	NT
Cervicovaginal carriage of								
Group B streptococci		NT	+	NT	NT	NT	–	NT
M. hominis		NT	–	NT	+	+	–	NT
U. urealyticum		NT	–	NT	+	+	–	NT

NT = not tested.
\+ = significantly correlated.
– = not correlated.

Study Locations: A: New Orleans[72] B: Baltimore[83] C: Winnipeg[13] D: Tucson[54] E: Gallup, New Mexico[12] F: San Francisco[119] G: Seattle[71]

dysuria, or lower abdominal pain. Findings of cervicitis (e.g., friability, erythema, cervical mucopus) have been noted rarely. Two studies found positive correlations with cervical ectopy.[72, 83]

Large longitudinal studies of chlamydial colonization during pregnancy are lacking. Harrison et al. showed a slight increase in cervical carriage in women in the third trimester compared to those in the first or second trimester (8.0 vs 7.1 per cent).[54] Heggie and coworkers studied 131 women serially and found 20 per cent were positive in the first trimester and 22 per cent in the third.[59] Nine per cent of women become newly infected, and 7 per cent reverted from culture positive to negative.

Immunologic Factors

The protective or pathogenic properties of humoral and cellular immunity to *C. trachomatis* are poorly defined in uncomplicated genital infections in nonpregnant women.[32, 61, 66] Even less is known of antichlamydial immunity during pregnancy. In general, more superficial mucosal infections such as urethritis, conjunctivitis, or uncomplicated cervicitis incite low levels of humoral immune response. In comparison, deeper infections, such as pneumonitis in infants, salpingitis, or lymphogranuloma venereum, result in measurably higher serum antibody titers. Genus-specific antibody, as measured by complement fixation, usually is detectable only in patients with LGV or salpingitis. Microimmunofluorescence (MIF) techniques are much

more sensitive and detect antibodies against species- , subspecies- , and serovar-specific antigens. Additionally, class-specific antibodies (IgG, IgM, IgA, sIgA) can be measured by MIF.

Some nonpregnant women with uncomplicated cervical chlamydial infection have no detectable humoral antibody response, but most have at least low-level MIF–IgG in serum.[32] In contrast, women with salpingitis often have high and serially increasing MIF titers. From 20 to 46 per cent of women with acute PID have had significant titer changes in IgG by microimmunofluorescence, with 17 to 38 per cent having positive IgM titers by MIF. As many as 62 per cent of women with acute salpingitis had MIF–IgG titers of greater than 1:64, and higher geometric mean titers (GMTs) correlated with more severe tubal inflammation noted at laparoscopy. Positive titers may persist for up to 6 years with little change,[94] but data on titer changes over time with repeated episodes of lower or upper tract chlamydial genital infections are not available. Significant MIF titers (>1:64) appear to be markers for prior chlamydial salpingitis in women with tubal infertility and in women with subsequent ectopic pregnancy.[17, 118]

Jones has recently reviewed the evidence that serum antibody is protective against genital chlamydial infection.[63] He reviewed data from Indianapolis indicating that attack rates of chlamydial urethritis or cervicitis were lower in patients with prior STDs or prior chlamydial cultures. Protective effects of prior chlamydial cervicitis appeared to be short lived, with decreased protection noted beyond 6 months. In vitro data suggest neutralizing roles for antibody directed against the MOMP of *C. trachomatis*; protection of cell cultures has been demonstrated with both polyclonal and monoclonal antibodies against MOMP.[25, 89] Antibody against MOMP, however, has been found commonly in infected male and female subjects, and no protective role has been attributed to this antibody in vivo.[63]

Data on the significance of IgA antibody in serum or in cervicovaginal secretions are incomplete and confusing. Cevinini et al. found that women with salpingitis had higher rates of serum IgA antibody (45.2 per cent) than those without known infection (5.2 per cent).[28] Examining uncomplicated cervical infections, McComb et al.[73] noted a positive correlation with local antibodies (IgG/IgA) in cervical secretions and positive chlamydial cervical cultures. However, Richmond et al.[102] found no good correlation between local cervical antibodies (IgG/IgA) and isolation of *C. trachomatis* from the cervix. In none of these studies was secretory IgA specifically detected. Brunham and colleagues[18] did find that the presence of sIgA (tested for by MIF utilizing antisecretory-component fluorescein-tagged rabbit globulin) was inversely correlated to quantitative recovery of *C. trachomatis* in cervical secretions. These workers suggested that such locally produced and secreted antibody may modulate cervical shedding of chlamydiae. Martin has studied the prevalence of serum and local antibody in pregnant women.[72] A positive local antibody to *C. trachomatis* was most predictive of cervical infection in young women

less than 20 years of age, but cervical antibody had a positive predictive value of only 64 per cent. While most women (97 per cent) with cervical infection were serum-antibody positive, many antibody-positive women did not have positive cervical cultures. The protective and diagnostic significances of serum, local, and secretory antibody in pregnant women deserve further study.

Recently, further attempts to clarify the protective versus pathologic roles of human antibody responses to *C. trachomatis* have centered on examination of antigen-specific antibody patterns using immunoblotting (Western blot) techniques.[82] Major antigens include those having genus-specific, species-specific, subspecies-specific, and serovar-specific epitopes.[1] Preliminary attempts have been made to characterize human immune responses to these antigens. Clear patterns of response to specific antigens in specific disease states have yet to be well defined. Most studies have identified antibodies to MOMP and to LPS in most adults with documented chlamydial genital infections,[19, 23, 27, 45, 82] although Jones and colleagues have found responses to MOMP to be variable and frequently absent in lower genital tract infections.[63, 82] In women with salpingitis, Gump et al. found reactions to MOMP, LPS, and the 60 Kd antigen in 8 of 8 subjects.[45] Jones found anti-MOMP antibodies in 2 of 7 women with endometritis, but 0 of 5 with cervicitis.[63] Brunham found that chlamydia-infected women with postabortal pelvic infection were less likely to produce antibody against 57 Kd or 60 Kd antigens than were chlamydia-positive subjects who escaped such postabortion infection.[23] These findings suggest that such antibodies may protect against ascending chlamydial infections but contrast with other findings from the same laboratory, indicating that seropositive women who have tubal infertility are *more likely* to have serum antibody against the 57 Kd antigen than are seropositive fertile women.[19] The relative protective or pathogenic properties of antibody against these chlamydial antigens obviously deserve greater investigation in pregnant women.

There have been limited examinations of the role of cell-mediated immunity in chlamydial genital infections. Cellular immune responses to chlamydial infections in forms of antibody-dependent cytotoxicity, generation of cytotoxic T cells, or activity of natural killer cells have not been identified. Brunham et al. identified lymphocyte transformation responses to chlamydial antigens (EBs or reticulate bodies).[21] These responses were studied in nonpregnant women with cervical colonization or infection defined by either positive isolation or serology. Mean stimulation indices were maximal in women with serum antibody to *C. trachomatis* (compared to culture ± antibody) and appeared to be relatively short-lived phenomena. These same workers studied 201 pregnant or recently pregnant women using the same lymphocyte transformation assays.[20] Lymphocyte transformation stimulation indices (LTSI) were significantly lower in chlamydia-culture–positive pregnant women than in culture-positive nonpregnant women and were depressed during the third trimester. Similar depressions in LTSI during pregnancy were noted in response to candidal

and streptococcal antigens and to PHA. The clinical significance of this depressed cellular immune response to chlamydial and other antigens during pregnancy is unknown.

In summary, serum and local antibodies against *C. trachomatis* may define women infected with this organism during pregnancy. However, few data on the protective effects of either humoral or cellular immunity versus chlamydiae during pregnancy are available. Little is known about the roles of antigen-specific antibodies in modulating the effect of this infection in pregnancy.

EFFECTS OF CHLAMYDIAL INFECTION ON PREGNANCY OUTCOME

For the past decade, the possibility that maternal chlamydial infection might affect the course of pregnancy and the health of the fetus adversely has been actively investigated. A number of findings give indirect credence to these possibilities. The following pieces of evidence suggest that chlamydiae might produce *in utero* infection or pregnancy morbidity:

1. Early studies at Boston City Hospital showed that abacteriuric pregnant women who received tetracycline had a lowered rate of prematurity than did similar women receiving placebo.[36] This result might have been due to therapy of clinically occult chlamydial infection (or other tetracycline-susceptible pathogens).
2. There is an inverse relationship between findings of fetal membrane and placental inflammation and gestational age.[33] Chorioamnionitis in this setting appears to be due to infection, but conventional aerobic bacteria have been isolated infrequently from placentas of premature infants.

   Several studies have isolated genital mycoplasmas (particularly *Ureaplasma urealyticum*) from placentas of preterm infants. For example, Kundsin et al. associated Ureaplasma placental membrane infection with low birth weight, histopathologic chorioamnionitis, and neonatal mortality, but did not isolate *C. trachomatis* from placentas of affected pregnancies.[65] Studies including adequate microbiology and immunohistology to demonstrate chlamydial placental infection are lacking.
3. Rettig and Altshuler[100] inoculated pregnant rats intraplacentally and intraamniotically with a DE strain of *C. trachomatis* and produced placental infection, chorioamnionitis, fetal pneumonia, and fetal deaths (Fig. 2). Banks and colleagues infected murine trophoblastic cells in vitro with a genital strain of Chlamydia.[5]
4. Harrison et al. have cultivated a chlamydial isolate from an infantile pneumonia case in primary amnion cell culture, supporting the possibility that this organism might infect amniotic cells in vivo.[57]
5. Several studies examining morbidity in infant populations born to infected women have found no excess of prematurity[39, 59]; other studies have not examined this possibility.[30, 47, 69] One British study of chlamydial conjunctivitis found that 42 per cent of affected infants were premature, compared with 15 per cent of chlamydia-negative infants.[97] However, this study included many infants in a premature infant nursery, suggesting a possible ascertainment bias in studying infants still in the hospital.

During the past 10 years, a number of studies have prospectively examined cohorts of infected pregnant women for a variety of adverse pregnancy outcomes.[12, 43, 53, 54, 60, 71, 116, 119, 120] Many have studied relatively small numbers of subjects and have failed to culture studied gravidas for other microorganisms.[60, 71, 116] Several have included larger numbers of subjects (433 to 4293),[12, 43, 54, 119, 120] have sought other microorganisms in the maternal genitourinary tract,[12, 43, 53, 54, 119] and have examined serologic responses (IgG and IgM) to chlamydial infection during pregnancy.[12, 54, 119] These studies have begun to elucidate the potential role of chlamydial infection in complications of pregnancy.

Martin et al. compared pregnancy outcomes in 18 chlamydia-infected women and 250 uninfected women.[71] Significant differences in adverse outcomes between chlamydia-positive and chlamydia-negative women were seen both in comparisons of the total population and in a matched-control analysis. Six of eighteen (33 per cent) chlamydia-infected women experienced stillbirths or neonatal death, compared with 3 per cent (8 of 238) of uninfected women. A matched-control analysis revealed significant differences between infected and uninfected pregnancies in percentage with low birth weight (28 vs 8 per cent), mean birth weights (2651 gm vs 3357 gm), duration of pregnancy (35.9 weeks vs 39.4 weeks), and gestational age of live-born infants (38.3 weeks vs 39.7). This study included relatively few women and examined no other cervicovaginal organisms but provided the first evidence that maternal chlamydial infection may result in poor fetal outcome.

Harrison and co-workers prospectively studied 1365 women at the University of Arizona (Tucson) with cultures and serologies for Chlamydia and for genital mycoplasmas.[54] Chlamydial cervical infection per se did not predict poor outcomes such as low birth weight, perinatal death, preterm delivery, or premature rupture of membranes. However, a subset of women who were culture positive for Chlamydia and had detectable IgM-antichlamydial antibody were found to have significantly increased rates of low birth weight (4 of 17 [23.5 per cent] vs 1 of 53 [1.4 per cent] chlamydia-positive, IgM-negative, and 52 of 793 [6.5 per cent] of chlamydia-negative subjects) and of premature rupture of membranes (7 of 17 [41.2 per cent] vs 4 of 53 [7.5 per cent] and 74 of 790 [9.4 per cent]). There were no differences between IgM-positive and IgM-negative chlamydia-infected women in terms of age or culture positivity for genital mycoplasmas. Women with *C. trachomatis* infection were very similar to those with *Ureaplasma urealyticum* colonization, and both groups shared many predisposing factors for preterm delivery: younger age, lower socioeconomic status, early age at first coitus, and low educational level. This study highlighted for the first time the importance of stratifying women with chlamydial cervical infection by IgM-antibody status. Women with IgM antibody presumably have recent infection; Harrison et al. hypothesized that this antibody also may reflect more in-

tense or invasive infection and so mark women at high risk for complications.

Two other studies have found correlates with adverse outcomes in the subset of infected women who have IgM antichlamydial antibody.[12, 119] Berman, Harrison, and colleagues studied 1204 Navajo Indian women, with a chlamydial prevalence of 22 per cent.[12] Women with chlamydial colonization did not have an increased rate of low birth weights, whereas a subset of women infected with *Mycoplasma hominis* did. However, 16 of 204 chlamydia-infected subjects had serologic evidence of recent infection, by IgM positivity or by IgG seroconversion.[6] Three of these 16 (19 per cent) were of low birth weight, compared with 6 of 133 (4.5 per cent) (relative risk 4.2) with "serologically chronic" infection. Sweet et al. performed a matched-control analysis of 270 chlamydia-infected and noninfected pairs of pregnant women.[119] There were no differences between the two groups of women in rates of preterm delivery, premature rupture of membranes, or newborns who were small for gestational age. In the subset of 67 women with IgM antibody to *C. trachomatis*, both preterm delivery and premature rupture of membranes were significantly more common (13 of 67 IgM-positive vs 8 of 99 IgM-negative subjects, $p = 0.03$, for each outcome).

Other studies have examined the role(s) of additional microorganisms in concert with *C. trachomatis*.[43, 53] A study of 115 pregnant adolescents in Baltimore[53] found 37 per cent infected with Chlamydia, 34 per cent with *Trichomonas vaginalis*, 38 per cent with Candida, and 90 per cent with *U. urealyticum*. Trichomonal infection (± candidal or chlamydial infection) significantly correlated with shorter gestation and low birth weight, whereas chlamydial or candidal infections alone did not carry an increased risk of these outcomes. Gravett et al.[43] examined 534 gravida for bacterial vaginosis (19 per cent prevalence) and chlamydial cervical infection (9 per cent prevalence). (The former condition was diagnosed on the basis of a biochemical profile of volatile short-chain organic acids in vaginal fluid characteristic of bacterial vaginosis; vaginal cultures for *Gardnerella vaginalis*, anaerobes, or *M. hominis* were not performed.) Bacterial vaginosis was associated significantly with preterm premature rupture of membranes, with preterm labor, and with amniotic fluid infection, but not with low birth weight. Chlamydial infection was independently and significantly associated with preterm ROM (odds ratio = 4.3), preterm labor (OR = 2.4), and low birth weight (OR = 2.7) by multiple logistic analysis. In neither of these two studies was the IgM-serologic status of women tested.

Finally, several other smaller studies from Chicago[60] and Norway[119] have found no differences in rates of perinatal mortality, preterm delivery, premature or preterm rupture of membranes, or low birth weight. None of these studies have included examination of IgM antibodies against chlamydia or have cultured for other microorganisms.

The possible mechanisms by which *C. trachomatis* might effect

these adverse outcomes are largely unknown. Ascending infection or chorioamnionitis due to Chlamydia in humans has not been described. Vaginal bleeding has long been known to be associated with preterm labor and delivery; Harrison et al. noted this association in their study.[54] Of more interest, Sweet and colleagues found that chlamydial cervical infection correlated with antepartum bleeding.[119] Of 270 chlamydia-infected women, 27 had bleeding, compared with 12 of 270 (4.4 per cent) culture-negative women [$p = 0.015$]). A similar association was found in a Norwegian study: 8.6 per cent (3 of 35) of chlamydia-positive women had had bleeding, compared with 7 of 546 (1.3 per cent) of culture-negative subjects.[116] The possible relationship of this association to preterm labor is unknown.

In summary, studies to date suggest that recent or severe chlamydial genital infections during pregnancy (as manifested by IgM antibody) in some women may be associated with complications of pregnancy, including stillbirth, preterm labor and delivery, and low birth weight progeny. The risk for these outcomes attributable to Chlamydiae is probably small; Berman et al. estimated that only 11 per cent of their Navajo women were at risk.[12] Other genital microorganisms, including genital mycoplasmas and the flora of bacterial vaginosis, may interact with *C. trachomatis* or may be associated with poor outcomes independent of Chlamydia. Current investigations, most notably an NIH-sponsored multiyear, multicenter study that is examining cervicovaginal flora and prematurity and that is scheduled for completion in 1989, should shed further light on these questions.

POSTPARTUM ENDOMETRITIS AND CHLAMYDIA

Over 40 years ago, Thygeson and Stone noted that "21 per cent of mothers whose babies had inclusion blennorrhea . . . [had] postpartum morbidity," an incidence more than twice the 8.7 per cent figure seen in all delivered women in their institution.[121] Rees reported an increased incidence of postpartum endometritis in chlamydia-colonized mothers,[97] as did Dunlap and colleagues.[34] Wager et al.[126] reported that 10 of 29 (34 per cent) chlamydia-infected women who delivered vaginally had intrapartum fever or late postpartum endometritis, compared with 23 of 300 (8 per cent) women without chlamydial infection [$p < 0.001$]). This association is not seen in women delivered by cesarean section.[126] Other studies have found similar associations of maternal chlamydial infection with late endometritis after vaginal delivery.[60, 120] However, several large studies have not found this asjsociation with either clinical endometritis or postpartum fever.[43, 54, 119] Recent studies have reported that cervicovaginal carriage of *M. hominis*, rather than Chlamydia, puts women at risk for these complications, either after vaginal[54] or cesarean deliveries.[12] Further studies using comprehensive microbiology (including characterization of bacterial vaginosis and its constituent mi-

croflora and measurement of chlamydial serologies) should clarify the role of *C. trachomatis* in postpartum maternal morbidity.

NEONATAL INFECTION WITH *C. TRACHOMATIS*

Several studies have focused on the rates of vertical transmission of chlamydia to neonates and on the development of neonatal infection syndromes (Table 3). Rates of transmission are relatively constant and are independent of the prevalence noted in the maternal population. Vertical transmission appears not to be influenced by maternal antibody status.[39, 59, 90, 111] Infection of the infant is acquired at the time of passage through the birth canal in most instances and has been reported following cesarean delivery only rarely.[40, 67] From 20 to 66 per cent of infants delivered to infected mothers will have positive conjunctival or upper airway cultures, and almost two thirds have serologic evidence of infection. Conjunctivitis occurs in 50 to 75 per cent of colonized infants, and 11 to 26 per cent may develop pneumonia. If there were a 6 per cent prevalence of chlamydial colonization nationwide, in a year with 3.2 million births, approximately 130,000 neonates would be colonized with at least 65,000 cases of conjunctivitis and 14,000 of pneumonia.

Chlamydial Conjunctivitis

The most common cause of ophthalmia neonatorum (neonatal conjunctivitis, defined as suppurative infection of the conjunctiva[e] during the first month of life) is *C. trachomatis* in developed countries. From 13 to 74 per cent of neonatal conjunctivitis is due to this organism (Table 4). Gonococcal infection is still prevalent in African and other developing areas, but chlamydial infection is also common. (Gonococcal infection in Western countries is rare because of effective prenatal maternal screening and treatment and effective postnatal prophylaxis of neonates.) Differing prevalences of Chlamydia may be attributable to different maternal population studies, different bases of neonatal populations studied (nursery vs ambulatory care facilities), and different detection methods (cytology, antigen detection, or culture).

Clinically, chlamydial conjunctivitis occurs 5 to 12 days postnatally, but this incubation period may overlap with the classic 3 to 5 days for gonococcal infection. Rarely onset of ocular infection may not be observed until 6 to 12 weeks of age. The first clinical signs may be a mild "sticky eye." As the infection progresses, there is a more purulent discharge, increased edema of both upper and lower lids, and frequent spread of the process to the other eye. Maximal inflammation, to the point of mucosal friability, occurs in the lower lid. Clinical severity should not be used to distinguish chlamydial infection from gonococcal or other causes and may range from mild mucoid discharge at the medial canthus without conjunctival erythema to profuse, bilateral purulent discharges with severe chemosis. Infants are

Table 3. *Prospective Studies of Perinatal Transmission of* C. trachomatis

LOCATION	NUMBER OF WOMEN	*CHLAMYDIA*-POSITIVE WOMEN (%)	*CHLAMYDIA*-POSITIVE INFANTS (Culture)	*CHLAMYDIA*-POSITIVE INFANTS (Serologic)	INFANTS WITH CONJUNCTIVAL INFECTION	INFANTS WITH PNEUMONIA
Seattle[30]	142	18 (12.7)	5/18	12/18	8	0
San Francisco[111]	5531	262 (4.7)	47/131	79/131	23	21
Boston[47]	322	6 (1.9)	4/6	NT	2	1
Cleveland[59]	1327	240 (18.1)	27/95	NT	20	3
Denver[39]	340	30 (8.8)	8/18	11/18	8	2
Malmo, Sweden[90]	1328	32 (2.4)	5/25	NT	4	0
Landskrona, Sweden[69]	273	23 (8.4)	5/23	NT	NT	NT

NT = not tested.

Table 4. *Etiology of Neonatal Conjunctivitis*

LOCATION	*CHLAMYDIA TRACHOMATIS*	*NEISSERIA GONORRHOEAE*	BOTH	TOTAL NUMBER OF INFANTS
Atlanta (1967–73)[2]	86 (28.5%)	43 (14.2%)	3	302
Liverpool (1973–76)[97]	33 (32%)	11 (10.7%)	3	103
San Francisco (1974–76)[104]	13 (13%)	0	0	100
Dallas (1977–79)[a]	24 (29.6%)	0	0	81
Malmo, Sweden (1978–81)[91]	35 (27%)	0	0	131
Seattle (1980–81)[107]	10 (18%)	0	0	55
Central African Republic[78] (1981)	5 (19%)	7 (26%)	0	27
Cleveland (1980–84)[58]	38 (74.5%)	0	0	51
Kenya (1983)[37]	20 (13%)	64 (43%)	6	149
Baltimore (1984–85)[96]	46 (46%)	0	0	100

[a] Rettig P: Unpublished data, 1979.

afebrile, and concurrent symptoms are unusual, although some infants will have mild rhinorrhea. From 20 to 83 per cent of infants with conjunctivitis will have positive nasopharyngeal cultures for Chlamydia.[7, 49, 58, 88]

A Gram's or Giemsa stain of the conjunctival discharge reveals a mixed population of polymorphonuclear leukocytes, lymphocytes, and mononuclear cells without bacteria. Either elementary body or reticulate body inclusions may be seen in the cytoplasm of conjunctival epithelial cells stained with Giemsa stain (Fig. 3).

Delay in initiation of therapy or lack of treatment due to improper diagnosis may lead to sequelae on ophthalmologic examination. Observed changes include mild punctate keratitis, conjunctival scars, and micropannus (marginal limbal neovascularity). Only rarely do these changes interfere with visual acuity.[42, 70, 79]

Diagnosis and treatment of chlamydial conjunctivitis are discussed below.

Chlamydial Pneumonia of Infancy

C. trachomatis is now recognized to be one of the most common causes of pneumonia during the first 3 months of life. Prospective studies have documented this cause of afebrile pneumonia in 15 per cent of infants in Dallas (Rettig P: Unpublished data, 1979) to 30 per cent in Seattle,[56] and 73 per cent in Chicago.[122] Differences among studies reflect different populations studied and different case definitions and case ascertainment methods. Rettig has recently reviewed the evidence for a causal role of *C. trachomatis* in this pneumonia syndrome.[99]

Infants are usually 3 to 11 weeks of age at presentation (Table 5). Prodromal symptoms are limited to mucoid rhinorrhea and, in 50 per

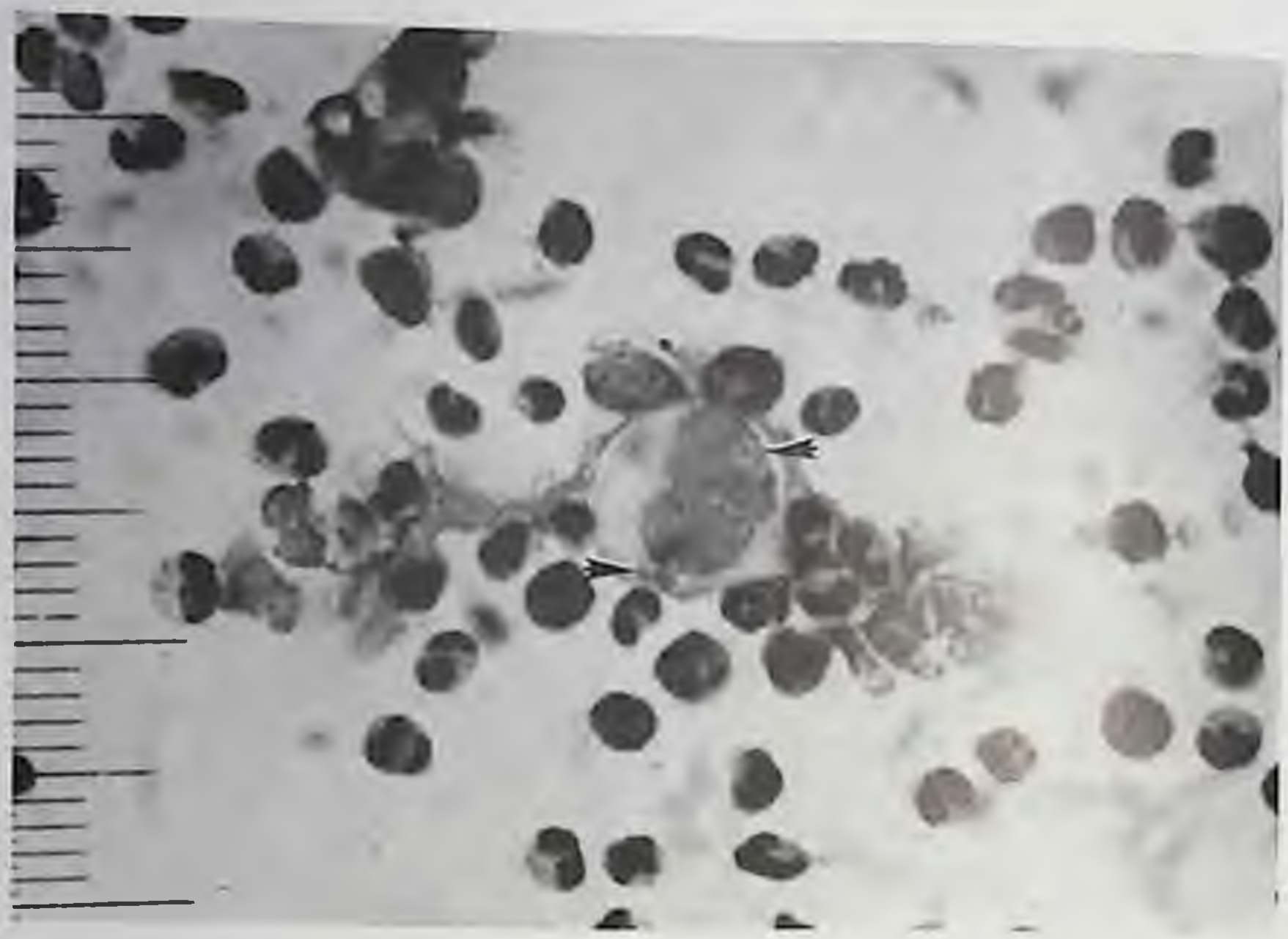

Figure 3. Conjunctival smear from infant with chlamydial conjunctivitis. Note mixed population of PMNs and lymphocytes. Arrows point to cytoplasmic chlamydial inclusions in conjunctival epithelial cells. (Original magnification 1000 ×.)

cent of patients, conjunctivitis. Onset of symptoms is usually gradual, often occurring over several weeks. Most infants are afebrile and have tachypnea and intermittent cough. The cough may consist of characteristic, staccato, repetitive paroxysms. Auscultation reveals diffuse rales without wheezes; prominent wheezing should suggest the alternative diagnosis of bronchiolitis. There may be concurrent middle ear effusion; these were noted in 24 of 41 infants in one series.[122] Chest radiographs usually show hyperexpansion with diffuse or streaky interstitial or alveolar infiltrates (Fig. 4).[95] Lab features are summarized in Table 5. Less frequent clinical pictures include wheezing, apnea, or bacterial superinfection.

Similar clinical pictures have been associated with pneumonia

Table 5. *Clinical and Laboratory Features of Chlamydial Pneumonia*

Onset at 3 to 11 weeks of age
Prior conjunctivitis (50%)
Staccato cough, greater than 1 week's duration
Afebrile pneumonia, with tachypnea and diffuse rales
Hyperinflation and diffuse interstitial infiltrates
Eosinophilia (50–65%)
Increased IgM
Increased serum IgG and IgA
Positive IgM-antibody to *C. trachomatis* by MIF

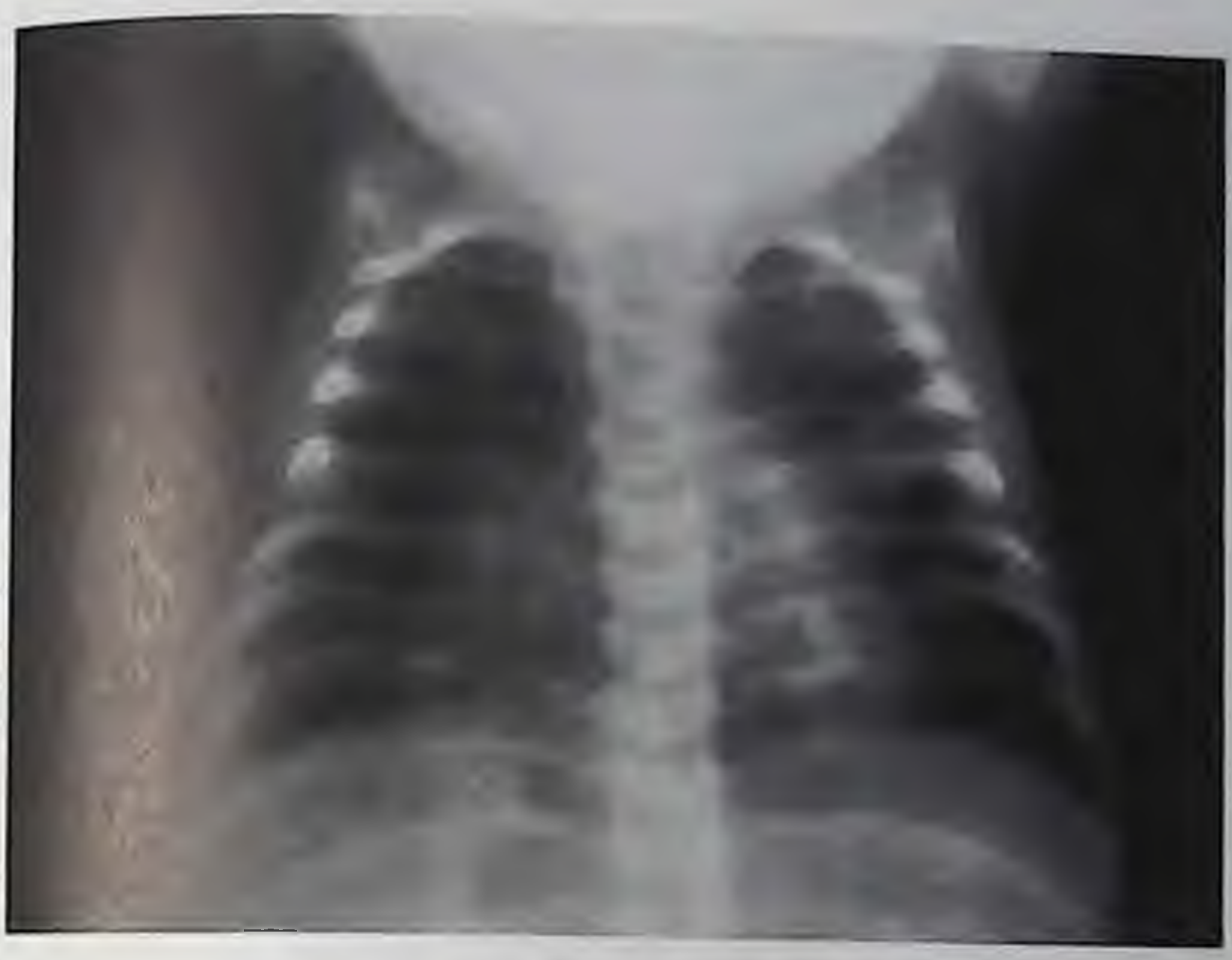

Figure 4. Chest radiograph of infant with chlamydial pneumonia. Note hyperexpansion and bilateral diffuse infiltrates.

due to cytomegalovirus, *Pneumocystis carinii*, or *Ureaplasma urealyticum*.[16] Viral coinfection is relatively common, particularly with cytomegalovirus (9 of 43 cases) or with respiratory syncytial virus (4 of 43 cases),[122] but infants with *C. trachomatis* alone have clinical illness similar in presentation and severity to those with viral coinfection. A specific etiologic diagnosis should be sought in all cases of the afebrile interstitial pneumonia syndrome of infancy because of different therapeutic implications of specific pathogens.

Occasionally, infants are ill enough to require ventilatory support for respiratory failure, but morbidity is usually mild to moderate. Infants may present with apnea. Poor weight gain, from inadequate caloric intake over several weeks, is frequent. Two reports recently suggested that infection in low birth weight infants may produce more chronic pulmonary symptoms.[3, 84] The natural history of untreated chlamydial pneumonia is gradual improvement over 4 to 8 weeks. Mortality is distinctly uncommon.

The long-term sequelae of chlamydial pulmonary infection in infants have been poorly defined (reviewed by Rettig in reference 99). Recently, Weiss and colleagues evaluated 18 children 7 to 8 years after chlamydial pneumonia of infancy.[128] Significant abnormalities in FEV_1, peak expiratory flow rates, forced expiratory flow rates, FRC, and residual volume/total large capacity ratios were all observed, when patients were compared with age-matched community controls. The obstructive changes responded to inhaled beta-adrenergic medication. Six of eighteen evaluated patients had a history of asthma,

compared with 1 of 19 control children ($p = < 0.03$). This study for the first time demonstrated the possibility that there are long-term pulmonary complications following infection in early infancy.

Convincing evidence that chlamydial infection in infancy at other body sites (vagina, gastrointestinal tract) produces clinical illness is lacking.[99]

DIAGNOSIS OF CHLAMYDIAL INFECTIONS

Cytologic Diagnosis

Cytology of conjunctival smears is highly specific and, in experienced hands, sufficiently sensitive (75–95 per cent) to provide rapid diagnosis of chlamydial ophthalmia neonatorum (see Fig. 3). However, this method requires considerable experience and has largely been supplanted by new rapid antigen detection tests (see below). Cytology of cervical scrapings (by Giemsa stain or on Pap smear) is too insensitive for adequate diagnosis. Brunham et al.[22] and Moscicki et al.[80] found that an increased number of polymorphonuclear leukocytes (>10 per high-power field) in cervical mucus of nonpregnant women was a sensitive, although relatively nonspecific, marker for chlamydial cervical infection. In pregnant women, Binns and colleagues noted that all 12 women with chlamydial infection had increased PMNs in cervical secretions, compared with 74 of 177 uninfected subjects.[13] This screening method requires further evaluation in pregnant women.

Serologic Diagnosis

Serologic tests are of little value in diagnosing cervical infection. Demonstration of IgM antibody by MIF or enzyme immunoassay techniques appears to be useful in making the diagnosis of chlamydial pneumonia.[93, 110] Positive IgM titers correlate with presence of pneumonitis and only rarely are seen in infants with conjunctivitis.

Culture Diagnosis

Isolation of Chlamydia in tissue culture is the preferred method of diagnosis and must be considered the "gold standard" to which all other methods are compared.[98] The sensitivity of a single culture is probably no more than 90 per cent; inadequate specimen collection, poor specimen handling, or specimen toxicity to cell monolayers may contribute to false-negative culture results. False-positive cultures may result from errors in interpretation of iodine stain (reading talc granules, epithelial cell glycogen, or precipitated stain as inclusions) or inexperience in interpreting immunofluorescence. Isolation of *C. trachomatis* from cervical or conjunctival secretions confirms infection at those body sites. Isolation of the organism from the nasopharynx in infants with typical lower respiratory tract symptoms provides presumptive proof of a chlamydial etiology for the pneumonia.

Antigen Detection Systems

In the past four years, two rapid antigen-detection methods using monoclonal antibodies have been introduced.[31, 114, 117] Direct fluorescein-tagged monoclonal antibody tests have sensitivities ranging from 70 to 100 per cent (in excess of 90 per cent in most studies) and specificities of 94 to 100 per cent.[31, 117] Differences in performance are attributable to adequacy of number of epithelial cells in the specimen, to the symptomatic versus asymptomatic status of the patient, and to the experience and expertise of the microscopist interpreting immunofluorescence. An enzyme immunoassay (Chlamydiazyme, Abbott Laboratories) has reported sensitivities of 81 to 98 per cent, with higher sensitivities in testing cervical specimens (90–98 per cent).[31] There are only limited experiences with these assays in pregnant women. Binns et al. found sensitivities of 96.6 per cent and 76 per cent, with specificities of 95.6 and 98 per cent, for Chlamydiazyme enzyme immunoassay and MicroTrak (Syva Company) fluorescent antibody tests, respectively, in 288 pregnant women.[13] Baselski and colleagues found sensitivities of 96.3 and 98.1 per cent and specificities of 92.9 and 95.4 per cent for Chlamydiazyme and MicroTrak techniques in a population of 255 pregnant women.[6] Advantages of the fluorescent antibody technique include ability of the technician to judge the specimen adequacy in terms of epithelial cells and to interpret morphology of false-positive fluorescent organisms. The major advantage of the enzyme immunoassay is the objective endpoint, which does not rely on the subjective interpretation of fluorescence. Either technique is probably sufficiently accurate to be substituted for culture in screening populations of pregnant women with high prevalence of chlamydial infection. These methods should be used only in settings with prevalences sufficiently high (? greater than 6–8 per cent) to ensure good positive predictive values and with tissue culture capabilities to allow periodic validation of test performance.

Several studies of rather small numbers of infants indicate that both the MicroTrak[10, 86, 96] and Chlamydiazyme[51, 52] methods have excellent performance in diagnosing neonatal chlamydial conjunctivitis and pneumonitis. The high sensitivities (93–100 per cent) observed in these clinical settings probably reflect the large numbers of infectious elementary bodies present in the conjunctivae and nasopharynx of infected infants. These methods should allow rapid and appropriate treatment of these syndromes.

TREATMENT OF CHLAMYDIAL INFECTIONS

A number of antimicrobials have in vitro activity against *C. trachomatis*.[15] Rifampin is the most active antimicrobial in vitro but is not indicated for clinical use. Tetracycline and erythromycin are active with minimal inhibitory concentrations (MICs) usually less than 0.5 μg/ml. The clinical relevance of "relative resistance" to erythromycin

Table 6. *Antimicrobial Therapy of Cervical Chlamydial Infection in Pregnancy*

ANTIMICROBIAL	DOSE	NUMBER OF WOMEN	MICROBIOLOGIC CURES	INFECTED INFANTS
Erythromycin base[92]	500 mg bid for 14 days	10	10/10	0/10
None	—	20	NS	9/20
Erythromycin ethylsuccinate[106]	400 mg qid for 7 days	43	38/43	5/42
Erythromycin[77]	500 mg bid for 10 days	38	ND	0/16
None	—	47	ND	5/21
Amoxicillin[11]	500 mg tid for 10 days	9	6/9	4/9
Placebo	—	6	2/6	4/5
Erythromycin[46] base	250 mg qid for 14 days	17	NS	0/17
None	—	22	NS	13/22
Erythromycin ethylsuccinate[114]	400 mg qid for 7 days	60	55/60	4/59
None	—	32	NS	12/24

NS = not stated; ND = not done.

(MIC of 1.0–2.0 μg per ml) has not been demonstrated.[81] Sulfonamides are quite active, and the addition of trimethoprim does not enhance this activity appreciably. Clindamycin is moderately active. Penicillins and ampicillin in vitro may inhibit inclusion formation, but are not chlamydiacidal and are of limited clinical use. Cephalosporins, aminoglycosides, and spectinomycin are inactive.

Treatment of Infection During Pregnancy

The considerable clinical experience with antibiotic treatment of nonpregnant adult women with chlamydial cervicitis contrasts with the paucity of data on treating these infections during pregnancy.[106] There are only a few small studies, using different dosage regimens and duration of treatment and having variable completeness of maternal and infant followup (Table 6).[11, 46, 77, 92, 106, 114] Only one small published study has included a randomly assigned placebo arm. The most extensive experience is that of Schachter, Sweet, and co-workers from San Francisco, who reported on treatment of 107 pregnant women (60 of whose infants were available for followup) with erythromycin ethylsuccinate, 400 mg q.i.d. for 7 days.[114] Ninety-two per cent of treated women had microbiologic cure, and only 4 of 59 infants born to treated mothers had neonatal chlamydial infection. Amoxicillin does not appear to have been effective in a small number of

women.[11] Treatment with a variety of erythromycin regimens has successfully interrupted transmission of chlamydial infection to the neonate. Few data are available on reduction of maternal morbidity, although McMillan et al.[77] found that 0 of 38 treated women, compared with 6 of 47 untreated, had postpartum complications attributable to chlamydial infection. A placebo-controlled trial of erythromycin during the 29th to 35th weeks of pregnancy is part of the current NIH-sponsored multicenter study and may clarify the role that treatment plays in decreasing adverse pregnancy outcomes.

Therapy during the latter weeks of pregnancy will significantly decrease transmission to offspring. It is difficult to recommend a specific dosage regimen or duration of treatment on the basis of available studies. Either erythromycin base, 250 or 500 mg q.i.d., or the ethylsuccinate, 400 mg q.i.d., for 7 to 10 days may be adequate. The estolate ester of erythromycin should not be used, as it is associated with hepatotoxicity during pregnancy.[74] Treatment of sexual partners should be included if the pregnant woman is sexually active during or after the treatment period.

Prevention and Treatment of Chlamydial Conjunctivitis

Attempts have been made to decrease the attack rate of clinical conjunctivitis by using forms of postnatal ocular prophylaxis other than silver nitrate, which appears to have no effect against development of chlamydial ophthalmia. Hammerschlag et al.[48] reported that topical erythromycin ocular ointment in the first hour of birth decreased subsequent chlamydial conjunctivitis in natally exposed infants. Of 36 exposed infants, 12 inoculated with silver nitrate developed conjunctivitis and 10 had subsequent nasopharyngeal colonization. Of 24 erythromycin recipients, 5 had nasopharyngeal colonization, but none developed conjunctivitis. Topical therapy therefore may decrease the attack rate of conjunctivitis, but does nothing to decrease the risk of later pneumonia. Topical tetracycline may not be as effective as erythromycin, based on indirect evidence from a large study in Dallas.[101] A study in progress in Brooklyn has yet to demonstrate efficacy for either topical erythromycin or tetracycline, compared to silver nitrate.[50] It is unlikely that a single application of any topical antimicrobial will prevent nasopharyngeal colonization.

Treatment of established chlamydial conjunctivitis has recently been reviewed by Rettig.[98] Topical therapy with erythromycin or sulfonamides fails to eradicate conjunctival colonization in 8 to 92 per cent of infants, and persistent or new nasopharyngeal colonization is common. Two studies have evaluated randomized topical vs oral therapy for chlamydial conjunctivitis. Topical or oral erythromycin therapies provided equivalent ocular clinical and microbiologic cures, but 8 of 19 topically treated infants had nasopharyngeal colonization, compared with 0 of 22 treated with oral erythromycin.[88] Heggie et al. compared topical sulfacetamide to oral erythromycin and documented microbiologic failure rates of 57 per cent after topical sulfacetamide, versus 6.7 per cent with erythromycin.[58]

Oral erythromycin, either (1) 10 mg per kg per dose of erythromycin estolate every 8 or 12 hours or (2) 10 mg per kg per dose of erythromycin ethylsuccinate q.i.d. for 2 weeks, is the currently recommended treatment of chlamydial conjunctivitis. Adjuvant topical therapy is not necessary because adequate tear levels of erythromycin are achieved after oral administration.

Therapy for Chlamydial Pneumonia

In an uncontrolled study, Beem et al.[8] showed prompt clinical improvement within 7 days of initiation of either erythromycin or sulfonamide therapy. Nasopharyngeal cultures reverted to negative within several days. Eleven infants who received only supportive care without any antibiotics had prolonged symptoms after presentation (10–51 days) and prolonged shedding of *C. trachomatis* from the nasopharynx. Other studies support the use of oral erythromycin for chlamydial pneumonia.[7, 36] A 2-week course of antibiotics is probably sufficient; no advantage has been demonstrated for longer duration of antibiotics.

SUMMARY

Much has been relearned and learned anew about perinatal chlamydial infections during the past 10 to 15 years. The adverse effects of infection on pregnancy outcome have been suggested but not fully documented or explained. Epidemiologic, biologic, and immunologic correlates of risk for infection and complications of pregnancy due to *C. trachomatis* are not yet fully understood. Increased appreciation of the importance of this organism in pregnancy, coupled with more facile methods for diagnosing infection and with further research using modern molecular techniques, promises to add greatly to the completeness of our knowledge and to our eventual complete control of this infection in pregnancy.

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Parasites and Pregnancy: The Problems of Malaria and Toxoplasmosis

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The parasites that afflict human beings are numerous and marvelously diverse. No niche in the human body is protected from parasites, including the transient niche of the pregnant uterus. Indeed, pregnancy does not protect against illness caused by any parasite capable of infecting humankind. The anatomic, physiologic, and immunologic perturbations of pregnancy can alter the clinical appearance and course of most parasitic infections. The many interactions of specific parasites and pregnancy have been recently reviewed.[1–4] This article discusses some general aspects of parasitic infection in pregnancy in order to provide a background for more detailed discussion of two important protozoan infections in the pregnant patient: malaria and toxoplasmosis.

PARASITES AND PREGNANCY

Not every parasite jeopardizes pregnancy and not every pregnant woman with parasites is ill, has a fetus at risk, or requires treatment.[5] The life cycle of the parasite in the human host, the quantity and the location of the parasite, and the host–parasite interaction determine the clinical expression of the infection and the need for treatment during pregnancy. An understanding of parasite life cycles is essential for evaluating the parasitized gravida (Table 1). As a general rule, drug treatment of parasitic infections during pregnancy should be used only when there is clear risk to maternal or to fetal health.

Some parasites spend their whole life on the surface of the human

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Table 1. *Residence of Parasite*

LIFE CYCLE IN OR ON HUMAN HOST	SURFACE DWELLERS	INVASIVE TISSUE DWELLERS
No maturation and no increase in parasite population	Ticks Maggots	Larva migrans: Toxocara sp., *Gnathostoma spinigerum*, *Dirofilaria immitis*, Trichobilharzia sp.
Maturation but no increase in parasite population	*Enterobius vermicularis* *Trichuris trichiuria* Taenia sp. *Diphyllobothrium lata*, *Fasciolopsis buski*	Hookworm sp. *Ascaris lumbricoides* Anisakis sp. *Dracunculus medinensis* *Fasciola hepatica* *Cysticercus cellulosae (T. solium)*
Maturation and increase in quantity of larvae or eggs but no increase of infective stage	*Tunga penetrans* Chiggers (Trombiculid mites)	*Angiostongylus cantonensis* *Trichinella spiralis* Filarial nematodes: *Wucheria bancrofti*, *Brugia malayi*, *Onchocherca volvulus*, *Loa loa* Schistosoma sp. *Clonorchis sinensis* *Opisthorchis viverrini* *Paragonimus westermani* *Echinococcus granulosus*
Maturation and reproduction with increase in quantity of infective stage, eggs, larvae, and adults	Pediculus sp. *Sarcoptes scabiei* *Giardia lamblia* *Trichomonas vaginalis*	*Entamoeba histolytica* *Toxoplasma gondii* Plasmodium sp. Babesia sp. Trypanosoma sp. Leishmania sp. *Capillaria philippinensis* *Strongyloides stercoralis* *Hymenolepis nana* *Echinococcus multilocularis*

body: the skin, genital tract, or the gastrointestinal mucosa. These organisms do not penetrate the surface barriers of the pregnant patient and thus are not an infection threat to the uterus or the fetus. For example, pinworms and scabies are annoying discomforts but do not by themselves pose a serious threat to the patient or her fetus. Some surface dwellers may produce local injury that can adversely affect the pregnancy. For example, Giardia can produce nutritionally disabling diarrhea, and Trichomonas may be associated with cervicovaginal infection that precipitates premature labor or premature rupture of the membranes.[6] Some ectoparasites like the body louse serve as vectors for other pathogens potentially harmful for pregnancy.

Parasites that penetrate surface barriers and invade the host's viscera are an infection threat to the fetus and the uterus. Such parasites may infect the fetus by direct penetration of the uterus and placenta or by transplacental transmission by way of the maternal bloodstream.[7] Trichinella and filarial nematodes may infect the intrauterine contents by direct migration and by the hematogenous route. Toxoplasma, malaria, and trypanosomes, blood-borne protozoa, all cause placental and fetal infection via the bloodstream. The inflammatory response to eggs, larvae, or adult parasites in the uterus or the placenta can injure placental function causing intrauterine growth retardation, fetal demise, and premature labor. Inflammatory or parasite masses may have adverse mechanical effects in the pelvis or birth canal, such as echinococcal cysts or schistosome egg granulomas.

Many parasites have obligatory life cycle stages away from the human host and the quantity of parasites can increase only if the host acquires additional inocula. Parasites that can increase in quantity within the human host, whether surface dwellers or invasive tissue dwellers, may be especially deleterious to maternal and fetal well-being. One pair of adult schistosomes can produce an enormous number of granuloma inducing eggs. Tissue-invasive parasites that can complete their maturation and reproduction within the human host, thereby increasing the parasite burden in the mother, in the placenta, or in the fetus, are the greatest threat to maternal and fetal well-being. The effect on the fetus of invasive parasitic infection in the mother is determined by the immune status of the mother and the fetus, by the intensity of maternal parasitemia, and the quantity of the fetal inoculum (Fig. 1). The small hookworm, *Strongyloides stercoralis*, can complete its life cycle in the human host. The adult worm lives in the duodenum and proximal small intestine. During pregnancy, reduced gastrointestinal motility allows the eggs to hatch and the larvae to complete their transition to infective filariform larvae, which can penetrate the distal gastrointestinal mucosa. Hyperinfection syndrome with gastrointestinal dysfunction and persistent eosinophilia due to the continuing circulation of increasing numbers of tissue-invasive Strongyloides larvae can produce fatalities in pregnant and in immunodeficient patients.

Pregnancy is accompanied by alterations in cell-mediated immunity, a general relaxation of tubal structures, extraordinary hemo-

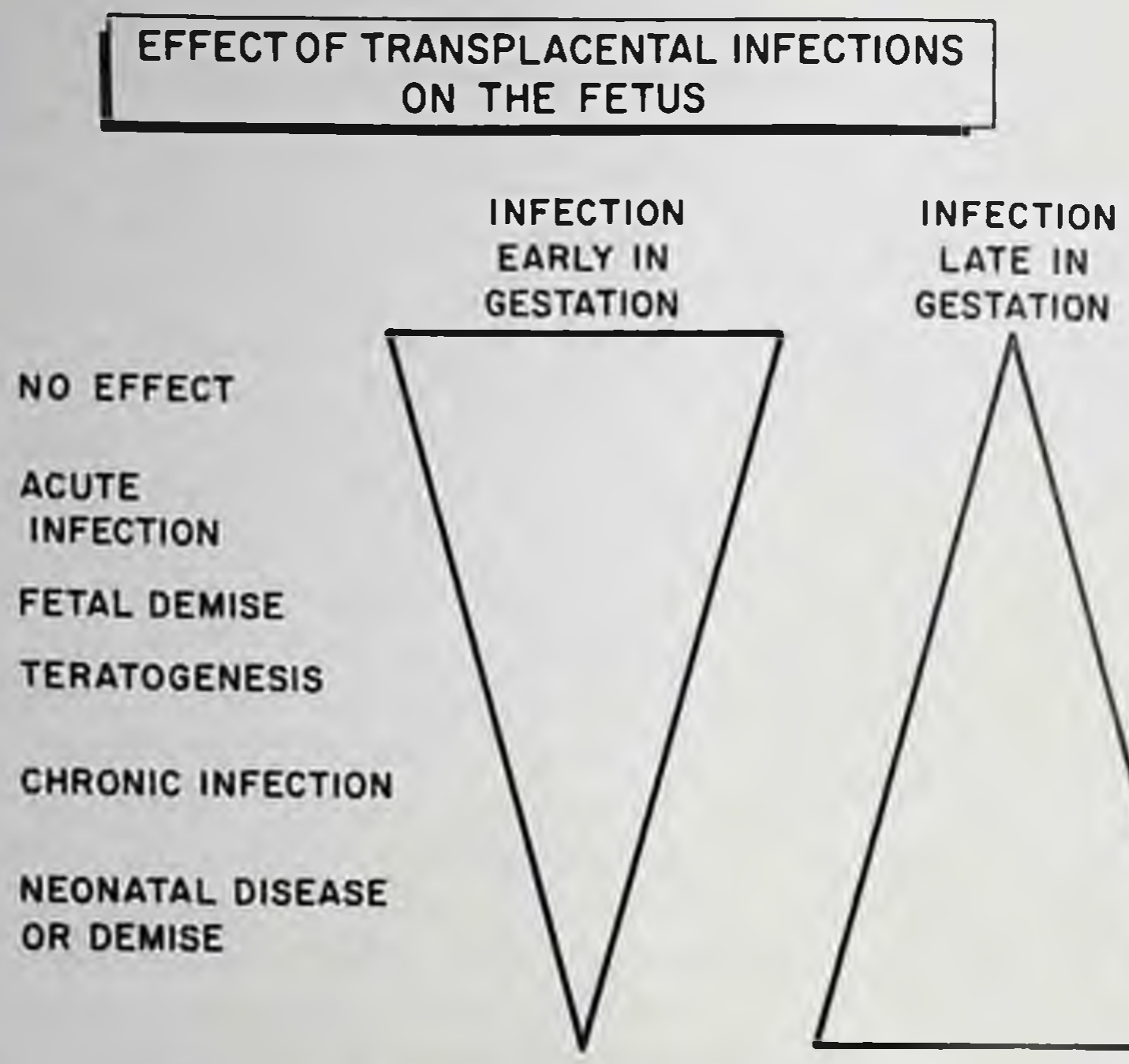

Figure 1. Infection of the mother early in pregnancy is most likely to have no adverse fetal effect because the fetus escapes infection. The small placenta of early pregnancy is an effective barrier to the transmission of pathogenic microbes. For the minority of fetuses infected, however, the results are almost always devastating: acute infection with fetal demise, abortion, or dysmorphic growth.

As the maternal–placental interface expands and ages, and the maternal–fetal milieu matures, the placental barrier becomes less effective. Transplacental infection during maternal parasitemia is more likely late in pregnancy so that fetal infection is more common. The effects of infection on the fetus are modulated by the maturing fetal immune response so that subclinical and clinical infections are more common than severe fetal disease or fetal demise.

dynamic readjustments, and enhanced nutritional requirements. Pregnancy can amplify the virulence of concomitant parasite infection. The pregnant patient with a hookworm burden that might not cause clinical problems in a nonpregnant patient may develop severe anemia and hypoalbuminemia. Parasites that injure maternal nutrition, such as Giardia and Strongyloides may cause profound disease in marginally nourished women. Diminished gut motility and cell-mediated immunity enhance susceptibility to gastrointestinal parasites and contribute to occasional cases of invasive amebiasis in previously asymptomatic obstetric patients. The importance of general maternal health and immune status in the clinical course of parasitic infection are well illustrated by malaria and toxoplasmosis.

Toxoplasmosis

Toxoplasma gondii is a global zoonotic parasite of felines. All species of cat may be infected. The domestic cat is the greatest source of human infection; however, tribal hunters of wild cats (jaguars, lions,

leopards) that do not keep domestic cats also have a high incidence of infection. *Toxoplasma gondii* infection occurs in all mammals and some avian species, especially ground-feeding birds. Obstetricians must be alert to the ubiquity of toxoplasmosis, to the risk of cats to pregnant women, and to the possibility that *Toxoplasma gondii* can cause devastating intrauterine infection during silent or clinically vague maternal disease.

The parasite has three distinct life cycle phases: the tachyzoite, tissue cyst, and oocyst.

Oocysts are produced in the feline gastrointestinal epithelium following a sexual reproductive cycle. Oocysts are excreted in feces and undergo sporogeny. Oocysts are resistant to a variety of physical and biochemical agents but will not sporulate below 4° or above 37°C. The sporozoites formed in the oocysts are infective for humans and a vast array of wild and domestic animals; under favorable conditions they may remain infectious for a year.

Ingestion of oocysts is followed by penetration of the gastrointestinal mucosa by sporozoites and circulation of tachyzoites, the ovoid unicellular organism characteristic of acute infection. Tachyzoites can penetrate many kinds of cells. They divide asexually and lyse infected cells. Tachyzoites remain viable for hours in extracellular secretions such as tears, milk, saliva, and peritoneal fluid. They are unable to survive desiccation, freezing and thawing, or digestive juices. Tachyzoites can be transmitted by blood transfusion, by needle stick, or across the placenta.

Tissue cysts form within cells that, for reasons as yet not clear, are not disrupted by the dividing parasite. Striated muscle and brain are the most frequent sites of tissue cysts but cysts can be found at any site. Tissue cysts can be present as early as the eighth day of infection and are presumed to persist, containing viable infectious bradyzoites, for the life of the host. Desiccation, freezing and thawing, and cooking destroy tissue cysts. When raw or improperly prepared flesh is consumed, the bradyzoites released from the tissue cyst are viable in digestive juices long enough to allow penetration of the gastrointestinal mucosa.

Infection with *Toxoplasma gondii* generates effective, protective humoral and cellular immunity. Specific IgM and IgG are regularly produced; however, because of the capacity of the organism to persist, the rate of decline of antitoxoplasma IgM is highly variable. In an immunocompetent host, the cycle of cell invasion and lysis with continued parasitemia is dampened and the parasite is confined to tissue cysts. Once infected, the immunocompetent host will inhibit the penetration and circulation of tachyzoites derived from ingested oocysts and tissue cysts.

In otherwise healthy adults acute infection is usually not clinically dramatic. If clinical symptoms do occur, the most commonly recognized illness is lymphadenopathy and atypical lymphocytosis, which may be accompanied by malaise, myalgia, headache, fever, skin rash, and splenomegaly. The posterior cervical lymph nodes are char-

acteristically involved; generalized lymphadenopathy may occur as well. The illness may be indistinguishable from mononucleosis caused by cytomegalovirus or Epstein-Barr virus.

The atypical lymphocytosis and febrile illness are transient, but the lymphadenopathy may persist for months. The persistence of tissue cysts may evoke little or no acute inflammatory response; however, alterations in immune function can disrupt the balance between the host and the encysted parasites. Severe immunodepression can result in reactivation of latent Toxoplasma infection. Toxoplasma meningoencephalitis and brain abscess are commonly seen, for example, in patients with acquired immunodeficiency syndrome resulting from human immunodeficiency virus infection. The immune modulation accompanying pregnancy, however, does not cause reactivation of latent toxoplasmosis.

Intrauterine infection is possible only when the mother has active toxoplasmosis with circulating tachyzoites. The risk of intrauterine fetal infection is confined to nonimmune mothers experiencing their primary infection and, rarely, to latently infected immunoincompetent mothers experiencing reactivation. There is no evidence from human and animal studies that latent *Toxoplasma* infection in healthy mothers causes congenital infection or abortion.

In the United States the prevalence of toxoplasmosis ranges from 20 to 70 per cent, depending on the area of the country and style of living, especially the keeping of pets. There is increasing frequency of positive serologic tests with increasing age regardless of sex. In the United States the documentable incidence of congenital toxoplasmosis is approximately 1 per 1000 live births. In one national survey, 38 per cent of women of childbearing age had antibodies to Toxoplasma.[8] Practitioners can expect that 50 to 60 per cent of their female patients reaching childbearing status could be susceptible to primary Toxoplasma infection.

Preconception toxoplasmosis testing and counseling are useful components of routine health care for childbearing women. A woman found to have antibody to Toxoplasma can be reassured about the rarity of intrauterine fetal infection. A woman found to be susceptible should be advised to avoid cats, cat litter, and uncooked meat, and urged to have repeat serologic tests performed during pregnancy. Common source outbreaks of toxoplasmosis among family, residential, and common interest groups are not unusual.[9] Clinical and serologic examination to identify subclinical infection of pregnant and nonpregnant women in the exposed group is of value. For example, we detected acute asymptomatic toxoplasmosis in early pregnancy in a woman without pet cats riding at a stable possessing infected cats associated with several human infections. As with rubella, all physicians share an obligation to alert women to the risks of toxoplasmosis and to pursue epidemiologic detection of cases.

The purpose of preconception and prenatal screening of susceptible women is to reduce the risk of acute maternal infection with the attendant risk of congenital infection and to identify the acutely in-

fected mother soon enough to choose appropriate management options. Studies in France[10,11] confirm the finding that women infected before conception had no evidence of abortions, stillbirth, or congenital infection caused by Toxoplasma sp. Among the offspring of 542 women acquiring toxoplasmosis during pregnancy, 61 per cent had evidence of congenital infection. In the affected infants, 6 per cent suffered perinatal death, 5 per cent had severe clinical disease, 9 per cent had mild clinical disease, and 41 per cent had subclinical disease. Abortion, perinatal death, or severe congenital infection occurred almost exclusively in the offspring of women infected early in pregnancy. As with other intrauterine infections, the risk of infection for the fetus and the severity of the disease produced are related to the time during pregnancy when maternal and transplacental infection occur (see Fig. 1). If the mother is infected early in pregnancy, transmission to the fetus is uncommon, but the disease produced is severe: abortion, severe congenital infection with teratogenesis, abnormal growth, or disabling residual. Transmission of Toxoplasma is most likely when maternal infection is acquired during the last trimester, but the illness in the child is more likely to be subclinical.

The clinician has three questions to ask about each pregnant patient: (1) is the patient susceptible and not infected?, (2) does the patient have an inactive, latent infection?, (3) does the patient have a recent, active infection potentially hazardous to the fetus? A simple in vitro method of culturing the organism regardless of the stage of the infection does not exist. Inoculating blood or other fluids containing tachyzoites into animals provides positive identification but is useful only during acute infection and is available only in some centers. Diagnosis depends on serologic tests, chiefly the indirect fluorescent antibody tests for antitoxoplasma IgG and IgM. The Sabin-Feldman dye test and newer ELISA tests may be used, but most contemporary protocols for serodiagnosis emphasize the IgG and IgM IFA tests.

Because the rise and fall of antitoxoplasma antibodies vary from case to case it is best to follow the results of two or more sets of tests. The probability of recent infection is high if the IgM titer is high (200 IU/ml or 1:512 or more). The probability of recent infection is highest if the IgG titer is 1:1024 (1000 IU/ml) or more and the IgM titer is 1:256 or more. Table 2 provides the author's recommendations for obtaining and interpreting Toxoplasma sp. serologies in the pregnant patient.

When recent or active infection is documented, the patient and her physician have three options. Early in pregnancy, if obstetric and ethical conditions permit, the patient may elect to terminate the pregnancy. Careful monitoring of the fetus and withholding antiparasitic drug therapy are options especially if infection occurred early in pregnancy and the fetus appears to be thriving. Treatment of acute maternal toxoplasmosis appears to reduce the risk of fetal wastage and congenital infection. It would be this author's choice to treat an actively infected patient at any stage of pregnancy if the patient wishes

Table 2. *Management Strategy for Toxoplasma Serologic Testing During Pregnancy*

STEP		GO TO STEP
1	Serologic testing before conception or at first prenatal visit.	2
2a	If negative IgG, the patient should be retested at 18–22 weeks.	6
2b	If positive IgG, immediately repeat tests including IgG and IgM.	3
3a	If IgG positive, stable, or low titer, IgM negative, suspect old or preconception exposure. Repeat tests in 2–4 weeks.	4
3b	If IgG positive, any titer, IgM positive, suspect recent exposure. Repeat tests in 2–4 weeks.	5
4a	If repeat IgG positive, titer stable, IgM negative, confirm old exposure. No further testing necessary.	—
4b	If repeat IgG positive, titer rising, IgM positive, suspect recent exposure. Repeat tests in 2–4 weeks.	5
5a	If repeat IgG and IgM positive (stable or declining titer), suspect recent exposure 2–6 months before tests obtained. Treat according to gestational age at time of presumed infection and according to patient wishes.	—
5b	If repeat IgG and IgM positive with rising titers suspect active recent infection. Treat according to gestational age and patient wishes.	—
6a	If repeat serologic tests negative, repeat tests at 36 weeks.	—
6b	If repeat serologic tests positive, go to step 3.	3

to continue the pregnancy. Spiramycin, a macrolide antibiotic related to erythromycin, has been used throughout pregnancy in Europe and Canada without adverse effects on mother and fetus. It is available in the United States only by special arrangements but can be obtained by contacting the Centers for Disease Control in Atlanta, Georgia. Both spiramycin and Toxoplasma tachyzoites are present in breastmilk. A recently infected nursing mother can be treated with spiramycin without risk to the child. Pyrimethamine and sulfonamides are effective but potentially teratogenic and should be used only after the first trimester.

Malaria

Malaria is caused by four Plasmodium spp. transmitted by the bite of female Anopheles mosquitoes and is characterized by relapsing fever, rigors, splenomegaly, and anemia. Malaria is endemic in many parts of Africa, Asia, and Central and South America, where the environment and the culture support the breeding of mosquito vectors and encourage frequent contact between mosquitoes and humans. Over 5000 cases of malaria were imported into the United States between 1978 and 1982.[12] In 1984 alone, 1007 cases of malaria were reported in the United States.[13] Thirteen babies with congenital malaria were reported in the period from 1980 to 1981.[12] In 1984 the only case of malaria acquired in the United States was an infant with congenital malaria.[13]

When a female Anopheles mosquito bites an infected human,

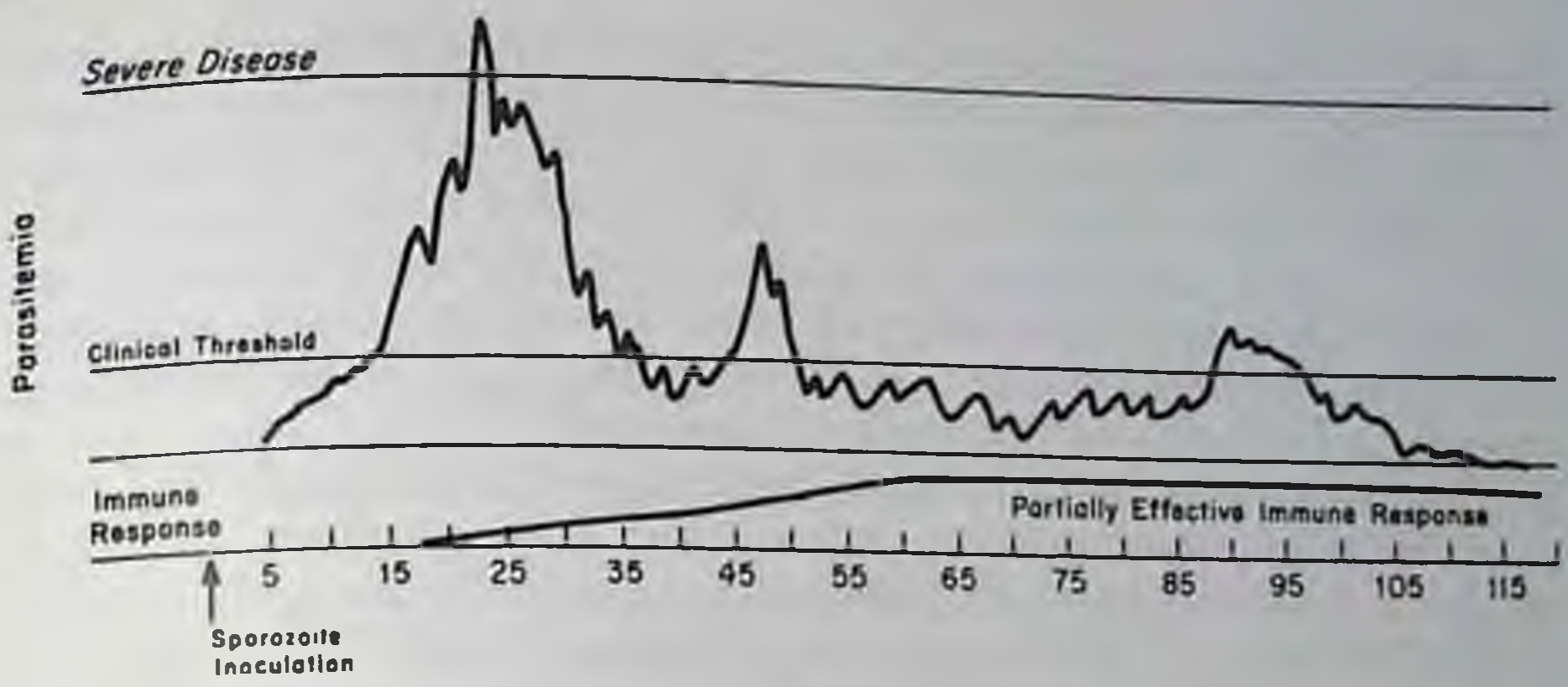

Figure 2. *The clinical course of P. falciparum malaria.* The appearance of clinical malaria is a function of the concentration of parasites. As the host immune response develops, the concentration of parasites in the blood declines below the clinical threshold. Pregnancy and parturition can alter the equilibrium between host and parasite. The depression of cell-mediated immunity associated with pregnancy may allow for recrudescence of clinical attacks. The placenta can sequester large numbers of parasitized red cells so that the infected patient with clinical malaria may have surprisingly few parasites seen in the blood. The redistribution of blood volume following labor and delivery may be attended by recrudescent malaria in the immediate postpartum period.

male and female gametocytes are taken into the mosquito's stomach. A sexual reproductive cycle taking about 2 weeks ensues, producing infective sporozoites that mature in the mosquito salivary gland. When the infected mosquito bites another susceptible human being, sporozoites are injected into the bloodstream and infect hepatic parenchymal cells. This preerythrocytic or exoerythrocytic phase, during which the parasite multiplies in hepatocytes, is usually not clinically apparent. Within 5 to 15 days merozoites are released from the liver into the bloodstream. Invasion of red blood cells by merozoites begins the cycle of asexual multiplication (schizogony) that results in the destruction of the parasitized erythrocyte. The intraerythrocytic, schizogony cycle takes 36 to 48 hours for *Plasmodium falciparum*, 48 hours for *Plasmodium vivax* and *Plasmodium ovale*, and 72 hours for *Plasmodium malariae*. When a sufficient concentration of parasites in the blood is in synchrony, the clinical cycle of periodic fever and destruction of red blood cells begins. The rigors and fever coincide with the rupture of red cells and the release of merozoites, and with the presence of gametocytes infective for mosquitoes.

The severity of the clinical disease produced by *Plasmodium* infection is related in part to the concentration of parasites (Fig. 2). The merozoites of *P. falciparum* will invade erythrocytes of any age, whereas *P. vivax* infects young red cells, and *P. malariae* infects older red cells. *Plasmodium falciparum* infection is characterized by high, rapidly increasing concentrations of parasitized erythrocytes. All Plasmodia spp. diminish the deformability of parasitized red blood cells.

However, *P. falciparum* infected erythrocytes develop membrane projections, assume unusual shapes, and become sticky. High concentrations of parasites and diminished red blood cell compliance produce obstruction to capillary flow with resulting tissue hypoxia. The brain, kidneys, spleen, and placenta are especially vulnerable to the accumulation of parasitized erythrocytes. Severe hemolysis, renal failure, coma, pulmonary edema, and intrauterine fetal death are features almost exclusively of *P. falciparum* malaria.[14]

In malarious areas infections begin in early childhood. Repeated inoculation of parasites serve as repetitive immunizations. After 5 to 10 years of residence in an endemic area, a youth has sufficient immunity to reduce the severity and duration of repetitive clinical attacks. Both antibody and cell-mediated immunity contribute to the disappearance of parasites in the blood.[15] Maternal antibody has been shown to protect the neonate from mosquito transmitted infection. Antimalarial IgG given to infected patients reduces the severity of the illness. As time passes the infection may be clinically manifest by splenomegaly, hyperglobulinemia, elevated antimalarial antibodies, and brief episodes of low concentration parasitemia. Immune complex nephrotic syndrome is a well-documented complication of chronic infection by *P. malariae*.

The interaction of malaria and pregnancy is influenced by the infecting Plasmodia sp. and the immune status of the mother. Nonimmune women have a more severe acute disease from any of the human Plasmodia than immune residents of a malarious region. Numerous clinical observations indicate that pregnancy exerts a dampening effect on the immunity to malaria.[16,17] Disruption of the host parasite balance by malnutrition, intercurrent illness, and/or pregnancy may precipitate recrudescent clinical illness. Parasitemia and parasitization of the placenta are more likely and more intense in primiparous mothers. In endemic areas, clinical attacks occur more frequently during pregnancy than in the nonpregnant state. The new multiple drug–resistant strains of *P. falciparum* have caused severe maternal disease and fetal wastage without regard to the mother's nutritional or immune status in Africa and in southeast Asia.

Maternal malaria can cause profound anemia, predispose to serious intercurrent illness, and promote placental insufficiency, causing intrauterine growth retardation, prematurity, low birth weight, abortion, and stillbirth. Fever, dehydration, and placental infection contribute to the onset of premature labor. In areas of Africa and Central America, maternal malaria is the most important infectious cause of low birth weight. Many studies demonstrate an increase in birth weight when mothers are given antimalarial therapy. In endemic areas malaria is a common cause of postpartum fever. A mother from an endemic area, not on malarial chemosuppression during pregnancy, should be treated during labor or immediately postpartum to avoid recrudescent disease that may be confused with endometritis or other postpartum infections.

Preexisting maternal immunity to malaria and the immune effects

of pregnancy modulate the effectiveness of the placenta as a barrier against fetal infection. Congenital malaria has been reported for all four Plasmodium spp. Congenital malaria may occur in the absence of any clinical evidence for malaria in the mother. The placenta may act like the spleen, sequestering large numbers of parasites. In one study from a malaria endemic region of west Africa, 40 per cent of mothers had demonstrable parasites in the blood, but 16 per cent of mothers had parasites found only in the placenta, not in the maternal or cord blood.[16] The incidence of congenital malaria in immune mothers residing in malarious areas is about 0.3 per cent. The incidence of congenital malaria in nonimmune mothers living in the same region is 1 to 4 per cent.[16] *Plasmodium falciparum* is the most common organism causing congenital infection, reflecting its predominance as the most common cause of maternal infection.

There is a disparity between the common finding of placental parasitization and the relative rarity of fetal infection. *P. falciparum* does not thrive in erythrocytes containing fetal hemoglobin. Maternal antibody coating merozoites may favor their rapid clearance by the fetal reticuloendothelial system. Soluble malaria antigens crossing into the fetus may elicit protective fetal IgM and cellular immune responses. The nondeformable, sticky, parasitized red cell may not be able to traverse the placental circulation to reach appropriate proximity to the fetal circulation.

As a general rule, clinicians working in endemic malarious areas can expect a high proportion of pregnant women to have malaria. Young primiparous women will have more severe clinical attacks and more intense placental infection than older multiparous mothers who are more likely to have subclinical infection. Congenital infection will be unusual but not rare. Women given malaria prophylaxis throughout pregnancy have larger placentas, larger babies, and less anemia than untreated women. Nonimmune mothers may be expected to have severe clinical attacks, intense parasitemia, and dense parasitization of the placenta with the risk of intrauterine infection and fetal death. Physicians to pregnant travelers or migrants to endemic malarious areas should regard the onset of any febrile illness within 2 months of exposure with suspicion.

Clinical attacks of malaria during pregnancy should be treated promptly. Maternal infection with *P. falciparum* should always be considered a life-threatening problem. The recommended treatment for all forms of malaria, except drug-resistant *P. falciparum*, is chloroquine phosphate, 1 gm initially followed by 0.5 gm after 6 hours and then once a day for 2 days. Because all species of human malaria except *P. falciparum* have a prolonged exoerythrocytic phase, primaquine phosphate 26.3 mg by mouth daily for 14 days should be given to prevent relapses. Primaquine should be used with caution, however, preferably after delivery. Drug-resistant *P. falciparum* should be treated with a regimen of multiple drugs including quinine.[18] Quinine is an insulin secretagogue and can precipitate hypoglycemia in pregnant patients who already have enhanced insulin secretion.[19] Newer

antimalarial agents such as mefloquine and quinghaosu are effective against multiple-drug resistant *P. falciparum*.[20] Considering the devastating effects of cerebral malaria, blackwater fever, and disseminated intravascular coagulopathy that seem to be more common in women with falciparum malaria during pregnancy, the use of these newer agents in pregnant patients is easily justified. Current treatment regimens can be obtained from the Malaria Branch of the Centers for Disease Control.

All antimalarial agents can have adverse effects on the fetus. Quinine is ototoxic and mildly oxytocic. Primaquine causes methemoglobinemia and hemolysis in susceptible individuals. Chloroquine can cause retinal and cochleovestibular damage. None of the other antimalarial drugs (sulfonamides, sulfones, tetracycline, pyrimethamine, and trimethroprim–sulfadoxine) are without potential hazard during pregnancy.

The best prophylaxis is to avoid malaria-infested areas. Conscientious chemoprophylaxis is mandatory if travel cannot be postponed until after delivery. The standard chemoprophylactic regimen is a weekly dose of 500 mg of chloroquine phosphate beginning 1 week before and continued for 8 weeks after leaving an endemic area. The trimethroprim–sulfadoxine combination is no longer recommended for routine prophylaxis because of occasional severe or fatal Stevens-Johnson syndrome.

CONCLUSION

In the United States, parasitic infection often may be regarded as exotic trivia by the busy practitioner; however, nothing could be farther from the truth. Toxoplasmosis is endemic, common, and a clear risk to successful pregnancy outcome. Malaria serves as a reminder that throughout the world arthropods and parasites continue to exact a particularly heavy burden on pregnant women.

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Antibiotic Therapy of the Newborn

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The subject of pharmacology was last reviewed in this periodical in 1981.[6] Since then, new antibiotics have become available, and there has been a continuing change in the organisms responsible for infection. The basic problem of early detection of neonatal infection and the administration of appropriate antibiotic therapy remains. This article addresses those areas of neonatal antibiotic therapy in which there has been progress since the earlier article and the important problems that have emerged.

INCIDENCE OF INFECTION

The incidence of serious sepsis in the newborn is uncertain. Estimates range from 1 to 10 per 1000 live births, but there is wide variation from unit to unit and it is believed that underreporting is common. Two recent studies[17, 43] reported that bacteria were isolated from the blood of more than 40 per cent of babies who dies during the first 28 days of life and that in two thirds of them the postmortem cultures provided the only evidence of infection. In contrast, a 10-year study in the United Kingdom[46] reported positive cultures at autopsy in only 32 of 835 (4 per cent) babies, many of whom were already known to have been infected. Clearly, any estimate of serious sepsis in the newborn must now include data on postmortem cultures.

It seems clear that the rate of neonatal sepsis is rising. In the Hammersmith Hospital, London neonatal bacteremia was found in 1.6 per 1000 hospital births in the years 1965 to 1975, and this rose to 5.7 per 1000 births during the period from 1976 to 1979.[2] In the Yale–New Haven Hospital the rate rose from 1 per 1000 in the period

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from 1966 to 1967 to 3.9 per 1000 live births in the period from 1974 to 1975.[20] Similar results were reported from Stockholm,[3] where the incidence of septicemia rose from 1.4 per 1000 live births during the period from 1969 to 1973 to 3.1 per 1000 live births in 1974 and 1978. The increase in septicemia is due in part to early-onset group B streptococcal (GBS) infection.[20] Because of the increased survival of highly susceptible low birth weight or preterm babies, the incidence of late-onset infection due to environmental microorganisms is likely to be higher than it was. There are no chronologic studies that compare infection in groups of babies matched for gestational age.

The incidence of infection is predictably higher in preterm babies and in those whose mothers had obstetric complications. Modern neonatal intensive care, especially the presence of indwelling intravascular catheters, is associated with an increased risk of sepsis.[30, 50] The risk of infection is much higher among babies of less than 1000 gm birth weight.[11, 32] There is a wide variation also in the rate of complications, including meningitis, that are consequent on an episode of neonatal septicemia. It is widely quoted that meningitis occurs in up to a third of cases of neonatal septicemia. It appears to be less frequent than this in the United Kingdom, although there are little recent published data on the subject.

It is very difficult to estimate the mortality and morbidity associated with serious sepsis in the newborn because in very few cases is infection the only problem. However, although antibiotic therapy has had a dramatic effect on the successful treatment of infection, there also has been an improvement in other aspects of intensive care.

EPIDEMIOLOGY

Changes in the pattern of microorganisms responsible for infection also will affect the mortality and morbidity rates. In many centers[2, 8, 51] coagulase-negative staphylococci are now the most common causes of bacteremia in the newborn. Infection with these organisms is accompanied by a lower mortality rate than infection with gram-negative bacteria[2] and the group B streptococci. In most reports, infection by coagulase-negative staphylococci occurs in babies more than 48 hours old, when the mortality would in any case be expected to be lower than in early-onset sepsis. However, Battisti et al.[2] reported that coagulase-negative staphylococci were the most common blood culture isolates for both early- and late-onset infection during the period from 1976 to 1979. Infection with these organisms is associated with the use of intravascular catheters, especially in small preterm babies. The increasing incidence of coagulase-negative staphylococci among blood culture isolates, coupled with the possibility that these organisms may be responsible for neonatal enteritis[23] and the suggestion that it is one of the bacteria involved in necrotizing enterocolitis,[9, 18, 23, 31] dictate that any antibiotic regimen for the newborn, especially those more than 4 days old, must include agents active against this heterogeneous group of organisms.

Table 1. *Sources of Bacteria Pathogenic to the Newborn*

MATERNAL GENITAL TRACT	ENVIRONMENT	BABY HANDLERS
Group B Streptococci	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
Escherichia coli	Serratia species	*Staphylococcus epidermidis*
Staphylococcus aureus	Citrobacter species	Haemolytic streptococci
Neisseria gonorrhoeae	Klebsiella species	*Branhamella catarrhalis*
Proteus species	Enterobacter species	Enterococci
Listeria monocytogenes	Proteus species	Salmonella
Mycobacterium tuberculosis	Clostridium species	
Clostridium perfringens	*Legionella pneumophila*	
Haemophilus influenzae		
Streptococcus pneumoniae		
Streptococcus milleri		
Mycoplasma hominis		
Ureaplasma ureolyticum		
Chlamydia trachomatis		

There is a wide variation also in the incidence of sepsis due to GBS. In some centers, where these organisms are a major cause of sepsis in the newborn, prophylactic penicillin has been given to all mothers. This has had a dramatic effect in reducing the rate of GBS infection.[34] In the United Kingdom the incidence of GBS sepsis is low, so that in most centers the use of prophylactic penicillin cannot be justified. Instead, high-risk factors such as maternal peripartum pyrexia[4] are relied on to indicate those mothers and babies who may require prophylaxis. An alternative would be to restrict GBS prophylaxis to the infants of mothers who do not have serum antibodies to the strain of GBS isolated from their vaginal swabs.

The prevalence and antibiotic susceptibility of bacteria responsible for neonatal infection vary from unit to unit, and within a neonatal unit there may be dramatic changes in quite short periods. Some of these, such as the appearance of a multiple resistant strain of *Staphylococcus aureus* or an outbreak of infection affecting a number of babies will be easily recognized, but other changes become apparent only if careful records are kept on all cases of serious sepsis.

INFECTING BACTERIA

A very wide range of bacteria is capable of causing infection in the newborn. The common bacteria responsible for infection in industrialized countries, such as the United Kingdom, are shown in Table 1. The bacteria vary greatly between hospitals in the same area, between different regions of the same country, and between countries; it is essential that those compiling an antibiotic policy for a neonatal unit should be fully aware of the common bacteria isolated within the unit and of those prevalent in the surrounding area. For example, neonatal infection with *Listeria monocytogenes* is uncommon in Great

Britain, but in France an antibiotic regimen must include agents active against this organism. Similarly, Flavobacterium sp., which causes problems in Southeast Asia,[53] is very rarely isolated from the newborn of western Europe. The group B streptococci, which are common causes of infection in some parts of America and Western Europe, are rarely responsible for infection in Mexico or Spain. There are also geographic variations in the antibiotic sensitivity of neonatal pathogens that have to be considered. These differences mainly occur as a result of local antibiotic usage. The sensitivity of the major neonatal pathogens to the antibiotics in current use and those that have recently been introduced are shown in Tables 2 and 3. The figures in these tables are taken from the literature and represent the extreme of the present situation. They may differ markedly from those reported in individual areas, thus reemphasizing that antibiotic strategy must be based on local information.[12]

In addition to the established pathogens that a fetus may encounter during the birth process, there is an increasing number of less common genital tract microorganisms that have the potential to cause neonatal infection. *Mycoplasma hominis*, which is present in the genital tract of 13 to 20 per cent of pregnant women,[16, 28] has been reported as a cause of meningitis in the newborn,[22, 25] subdural effusions,[49] pneumonia,[47] lymphadenitis,[45] and infections of the eye.[28] *Ureaplasma urealyticum* (T-strain mycoplasmas) also has been incriminated in fatal pneumonia of the newborn.[47]

Superficial infection with these organisms appears to be very low grade. Many of the cases reported by Jones resolved without antibiotic therapy, as did the case of lymphadenitis reported by Powell et al.,[45] once the pus had been aspirated. Tetracycline, 20 mg per kg per day was effectively used for meningitis by Gewitz et al.[22] after chloramphenicol and gentamicin had failed to eradicate the organism from the CSF. Ten days of treatment with chloramphenicol (50 mg per kg per day) also failed to sterilize a subdural abscess due to Mycoplasma in a 10-day-old baby. A number of other reports attest the efficacy of tetracycline in the treatment of mycoplasma infections in the newborn. The lipid-soluble tetracycline, doxycycline (Vibramycin) appears to be less effective.[25] In the case reported by Hjelm et al., the CSF was rapidly sterilized by lincomycin (30 mg per kg per day, divided 8 hourly and given by the intramuscular route). Dan et al.[5] found clindamycin (80 mg per kg per day) highly effective in eradicating mycoplasma from the blood and a burn site of a neonate. Erythromycin that is inactive against Mycoplasma sp. is probably the antibiotic of choice for the treatment of infections due to Ureaplasma. In most reported cases, however, the diagnosis has been made too late for treatment to be effective.

DIAGNOSIS OF INFECTION

Before a baby receives antibiotics, investigations for infection should be initiated. In our practice, this consists of a blood culture

Table 2. *Concentrations of Antibiotics (mg per liter) Required to Inhibit 50%:90% of Strains of Common Gram-negative Neonatal Pathogens*

	E. COLI	KLEBSIELLA SP.	ENTEROBACTER SP.	SERRATIA SP.	PROTEUS SP.	*PSEUDOMONAS AERUGINOSA*
Ampicillin	4:>128*	>128:>128	64:>128	>128:>128	2:>128	>128:>128
Azlocillin	4:>128	16:>128	4:>128	>128:>128	1:>128	8:64
Mezlocillin	2:>128	128:>128	4:>128	>128:>128	1:>128	32:>128
Piperacillin	1:>128	128:>128	4:>128	>128:>128	0.5:>128	4:64
Cefuroxime	4:8	2:4	4:>128	2:>128	1:>128	>128:>128
Cefotaxime	0.06:0.12	0.06:0.25	0.12:1	0.5:2	0.06:0.5	16:64
Moxalactam	0.12:0.5	0.12:0.5	0.25:8	0.5:8	0.25:1	16:32
Ceftriaxone	0.05:0.2	0.1:2	0.25:64	0.5:2	0.06:128	16:64
Ceftazidime	0.12:0.25	0.25:2	0.5:1	0.25:1	0.06:0.12	1:4
Gentamicin	1:2	0.5:64	0.5:32	128:>128	1:4	1:8
Netilmicin	1:2	0.5:32	0.5:32	8:13†	1:1	1:8

* Antibiotic concentration (mg/liter) inhibiting 50%:90% strains.
† Low inoculum.

Table 3. *Concentrations of Antibiotics (mg per liter) Required to Inhibit 50%:90% of Strains of Common Gram-positive Neonatal Pathogens*

	STAPHYLOCOCCUS AUREUS (β-LACTAMASE) POSITIVE	*STAPHYLOCOCCUS EPIDERMIDIS*	*STREPTOCOCCUS AGALACTIAE* (GROUP B STREPTOCOCCI)	ENTEROCOCCI	*L. MONOCYTOGENES*	CLOSTRIDIUM SP.
Ampicillin	1:128	1:>128	0.03:0.05	0.1:4	0.25:0.5	0.1:4
Azlocillin	2:>128	2:>128	0.03:0.05	1:4	1:2	0.25:4
Mezlocillin	2:>128	2:>128	0.03:0.05	1:8	1:2	0.25:4
Piperacillin	2:128	2:>128	0.03:0.05	2:8	2:2	0.12:8
Cefuroxime	0.25:1	0.1:4	0.03:0.03	>128:>128	>128:>128	
Cefotaxime	0.5:1	4:128	0.02:0.02	2:128	64:128	2:32
Moxalactam	4:8	32:>128	0.5:4	>128:>128	64:128	1:4
Ceftriaxone	3:6	3:25	0.05:0.1	>128:>128	12.5:>128	2:16
Ceftazidime	4:8	8:>128	0.1:0.2	128:>128	>128:>128	8:128
Gentamicin	0.25:4	8:32	16:32	4:64	32:32	128:>128
Netilmicin	0.25:4	0.1:1*	8:8*	1:2*	0.5:2*	128:>128

* Low inoculum.

and swabs from the ear and throat, and cultures of tracheal aspirate if available. Because of the low incidence of neonatal meningitis in the United Kingdom, it is not common practice to include a lumbar puncture in every septic screen, but only when there is a strong suspicion of meningitis.[35] Babies with bacteremia due to gram-negative rods or GBS have lumbar CSF collected 36 to 48 hours after the start of antibiotic therapy. A urine sample may be examined, but a diagnosis of urinary tract infection is only made on a suprapubic or catheter specimen. We have not found the routine examination and culture of gastric aspirates to be of value. Other microbiologic specimens are collected according to the clinical condition of the individual baby. Specimens are cultured with minimal delay, and if after 48 hours the cultures are negative and the baby is well, antibiotic treatment is stopped. Samples of CSF, heart blood, and bronchial swabs are collected aseptically on all babies who die. As well as confirming the efficacy of antibiotic therapy, the results of bacteriologic culture from these specimens contribute to the overall picture of infection within the neonatal population in the hospital and are of value even when a full autopsy cannot be carried out. In our experience, these specimens only infrequently show an infection that was not apparent before death.

Noncultural Methods

In recent years new methods have been developed for the rapid diagnosis of infection. Several research techniques have been applied to the problems of neonatal infection, and with the development of commercial "user friendly" kits, these have become available for assessment as routine investigations.

The noncultural methods available fall into two groups: those designed to rapidly detect small amounts of a specific bacterial antigen, and those that detect the physiologic changes in the host that are consequent on infection. It is largely these tests that require further investigation, for very little is known about the immune and other responses of the newborn to early infection.

Counter immunoelectrophoresis (CIE) is performed in agar gels, where the pH is controlled such that the antibody is positively charged while the antigen is negatively charged. Application of a voltage across the gel results in movement of the antigen and antibody toward each other. Precipitation occurs where they meet in optimum proportions.

Latex and coagglutination methods are slide agglutination techniques. In coagglutination, a strain of *Staphylococcus pyogenes* with protein A in its cell wall is mixed with specific antibody, such that the Fc portion of the immunoglobulin binds to the bacterial cell. When homologous antigen in a clinical specimen or bacterial culture is mixed with these cells, it binds to the Fab portion of the antibody and results in visible agglutination. The principle of latex agglutination is the same but uses latex particles (0.81 μm diameter) instead of bacterial cells.

Although these antigen detection methods have been applied to

the diagnosis of infection in older neonates, there are few reports of their use in premature babies.

The methods available for the detection of bacterial antigen or endotoxin have been dramatically improved with the advent of monoclonal antibodies. Techniques now permit the detection of antigen in raw specimens rather than to bacterial cultures only. Antigens can easily be demonstrated in urine or CSF and rather less readily in serum. There are few reports of these methods being applied to clinical samples of gastric or tracheal aspirates from babies, but they have been successfully used on adult sputum and on high vaginal swabs. The simplicity of the agglutination tests and their improved sensitivity has led to their widespread acceptance in clinical laboratories at the expense of CIE, which is now rarely used routinely.

The range of commercial reagents available is still not sufficiently comprehensive to cover all the major bacteria responsible for infection in the newborn, and at present there are no reagents for the recognition of coagulase-negative staphylococci, *Listeria monocytogenes*, or the Enterobacter/Citrobacter/Serratia group of gram-negative rods. Nevertheless, latex or coagglutination increasingly provides a means of rapidly diagnosing neonatal infection. False-negative, "prozone reactions" may occur if the sample contains excessive amounts of antigen. Samples giving negative results should therefore be retested at a 1 in 5 dilution.

PHARMACOLOGY AND PHARMACOKINETICS

In almost every respect the newborn baby handles antibiotics differently from older patients. To manage chemotherapy satisfactorily, the pediatrician must have access to neonatal data on the absorption, metabolism, distribution, and excretion of each antibiotic. It is not possible to extrapolate from data obtained in older children or adults; data from term babies are only of limited value in the management of preterm babies. Even when appropriate data are available, they cannot give the full picture because for ethical reasons, no data can be collected on healthy subjects. It is important to remember that not only is the dose per kilogram body weight different for neonates from adults, but that there are also differences in the type and degree of toxic side effects and the extent to which an antibiotic is protein bound.[10] Term babies may lack the enzymes required to de-esterify antibiotic esters, notably pancreatic lipase, which is required to convert oral chloramphenicol palmitate to the active agent. Hepatic enzymes necessary for the metabolism of antibiotics such as chloramphenicol also may be lacking, thus increasing the half-life with the consequent risk of drug accumulation.

Other drugs and antibiotics may affect antibiotic pharmacokinetics; thus, when penicillin is administered with chloramphenicol there are higher serum concentrations of chloramphenicol compared to those when it is used alone.[41] Theophylline has a diuretic effect that

may alter the rate of renal excretion of antibiotics, while furosemide, which is highly protein bound, will compete with antibiotics for binding sites. There are quantitative and qualitative differences between the serum proteins of newborn and older children; these differences affect the degree to which antibiotics are protein bound and thus their kinetics. With highly protein-bound antibiotics like cloxacillin this will have the effect of increasing the concentration of free (active) antibiotic in the circulation. It also will increase the rate at which the antibiotic is excreted.

Renal function in the newborn is different from that of older children. The glomerular filtration rate is 30 to 60 per cent of adult levels, and tubular excretion is also less. During the first 2 weeks of life there is a remarkable increase in renal function in term and preterm babies. These changes and the rates at which they occur have a profound effect on antibiotic pharmacokinetics. In addition, severe respiratory distress syndrome is associated with a reversible impairment of renal function and results in an increased serum half-life of antibiotics like the aminoglycosides, which are excreted via the kidneys. In the newborn the high proportion of total body weight that is water affects the distribution of antibiotics, and the changes in body water that occur during the first 2 to 3 weeks of life will significantly alter drug pharmacokinetics. Dehydration may easily occur in extremely low birth weight babies and in those receiving phototherapy or radiant heat; this will also affect pharmacokinetics, as does the increased permeability of membrane systems, low muscle mass, and instability of the peripheral circulation. Other factors, notably fever, anemia, and the method and type of feeding, affect drug pharmacokinetics and contribute to the very wide within and between patient variation that is observed during the first weeks of life.

The pharmacokinetics of five antibiotics that we have studied in comparable groups of neonates with clinical evidence of sepsis are shown in Table 4 together with data collected from the literature on the pharmacokinetics of other antibiotics in the newborn. Work from different centers appears to produce contradictory results. These differences are apparent rather than real and usually arise because differences in the postnatal ages of the study populations are reflected in changes in serum half-life and total body clearance during the first 2 weeks of life. During the first 3 days of life the elimination half-life of betalactam antibiotics is four or more times that observed in children and adults, and the rate of clearance is a quarter of that found in adults. Renal function improves dramatically during the first days of life with the result that the rate of total body clearance increases and the half-life decreases. At 2 weeks of age the half-life is approximately twice that of adults. Differences between the newborn and the adult with other antibiotics are not so extreme. The exceptions are the occasional babies who do not metabolize chloramphenicol or those with impaired renal function who do not excrete antibiotics like the aminoglycosides. In these cases the half-life may be exceptionally

Table 4. *Pharmacokinetic Data on New Antibiotics in Neonates*

	DOSE (MG/KG)	ROUTE	PEAK SERUM LEVEL (MG/L)	TROUGH SERUM LEVEL (MG/L)	SERUM HALF-LIFE (H)	VOLUME OF DISTRIBUTION (ML/KG)	TOTAL CLEARANCE (ML/MIN/KG)
Ceftazidime*	25	IM/IV	73	17	8.6	450	0.8
Cefuroxime*	25	IM/IV	45	10.5	5.8	671	1.6
Cefotaxime*	50	IM/IV	87	8	3.1	559	1.7
Ceftriaxone*	50	IM/IV	149	54	15.5	325	0.3
Moxalactam*	50	IM/IV	100	28	6.8	503	0.9
Azlocillin	50	IM	100–200	—	2.5	330	—
Mezlocillin	50	IM	80–150	—	2.1	520	—
Piperacillin	50	IM	115	—	3.5	400–580	—
Gentamicin†	2.5	IM/IV	7.5	2.3	7.9	637	1.0
Netilmicin	2	IM	5.7	2.2	—	—	—

* Data from de Louvois et al.
† Data from Mulhall.

long, and, because of drug accumulation, toxic serum concentrations may persist for days.

POLICY

The antibiotic policy employed within a neonatal unit must be tailored to fit local needs and be sufficiently flexible to allow for prompt modification if susceptibility patterns suddenly change. The antibiotic regimen for initial blind treatment in cases of suspected neonatal sepsis cannot provide cover for all possible pathogens. Value judgments have therefore to be made regarding the importance of some pathogens in the overall picture of infection within the individual NICU and whether it is necessary to guard against bacteria that may only rarely be responsible for infection. In the United Kingdom, where listeriosis affects fewer than 1 per 30,000 babies each year, it is not reasonable for pediatricians to strictly tie themselves to an ampicillin and gentamicin regimen (the optimal therapy for listeriosis) when a high proportion of the coliforms and staphylococci commonly responsible for infection are resistant to one or both of these antibiotics. Equally, in units that do not have a persistent problem due to infection with *Pseudomonas aeruginosa* the routine use of piperacillin or ceftazidime as initial therapy cannot be justified. With the increasing resistance of many neonatal isolates to ampicillin or gentamicin and in the absence of major local problems with Listeria or Enterococci, it is debatable whether this combination is still the treatment of choice for the septic newborn. During the last 8 years the NICU at Queen Charlotte's Maternity Hospital has relied on monotherapy with third-generation cephalosporins in the initial treatment of neonatal sepsis.[13–15, 27, 44] The clinical results with all of these agents have been very good. We have not observed resistance developing during treatment, nor have microorganisms with acquired or inherent resistance become a problem in the unit. On the results of in vitro testing, more of the organisms isolated from cases of serious sepsis have been susceptible to the third-generation cephalosporins used than to the ampicillin/gentamicin combination. In a few extreme cases gentamicin has been added to the cephalosporin prescription since the newer compounds do not exhibit the renal toxicity found when first-generation cephalosporins are combined with an aminoglycoside. As a result of this antibiotic policy the use of aminoglycosides within our neonatal unit has decreased dramatically, vancomycin usage has been kept to a minimum, and expenditure on the routine monitoring of these compounds has been correspondingly reduced. Cephalosporin monotherapy has been used successfully in other units also.[24, 29]

BLIND THERAPY

Twenty years ago, the combination of ampicillin and cloxacillin was used for babies requiring blind antibiotic treatment because of

the prevalence of *Staphylococcus aureus*. During the 1970s this became less common and resistance to ampicillin began to appear among the enteric gram-negative rods. Gentamicin, having been previously reserved for life-threatening infections and the treatment of known serious sepsis, was then introduced as first-line antibiotic cover, in combination with penicillin or ampicillin, depending on whether GBS or coliforms were considered to be the greater problem. This choice was made largely because of the absence of suitable alternative antibiotics at that time. There are now a number of antibiotics that may be considered as alternatives to the combination of ampicillin or penicillin plus gentamicin, and the role of these agents in neonatal practice needs to be considered.

The major groups of antibiotics that may be used in therapy of the newborn can be divided into two groups: those that may be considered for use as initial blind therapy such as a penicillin plus an aminoglycoside or a third-generation cephalosporin; and those that are confined to the treatment of specific infection such as chloramphenicol or erythromycin.

It is convenient to distinguish between initial chemotherapy prescribed before infection is confirmed and that given to babies with established infection due to a known organism. The antimicrobial agents used routinely for blind therapy must in most cases be appropriate for the treatment of the bacteria isolated. In a minority the regimen should be adequate but not the treatment of choice; treatment may then be changed to specific therapy. On only very rare occasions should the regimen be totally inappropriate for treatment of the microbe isolated. Antibiotics used for blind therapy should be active at the MIC_{90} level; that is, 90 per cent of bacterial isolates of the species concerned should be sensitive to the antibiotic. Some antibiotics are active against only 50 per cent of isolates (MIC_{50}), and these are not suitable for blind therapy. This problem does not arise with specific therapy where the in vitro sensitivity of the organism can be determined before treatment starts. It is not appropriate to regard the treatment given to babies with clinically suspected sepsis as a form of prophylaxis. Positive bacteriologic cultures will be obtained from many such babies, while others will respond to chemotherapy in a way that strongly suggests that there has been an infectious process even though cultures were negative. Antibiotics are sometimes used prophylactically in the newborn, for example, in babies with multiple chest drains, or in those undergoing surgery or repeated exchange transfusions.

Although there is increasing evidence that aminoglycoside-induced ototoxicity in the newborn is rare, it is still common practice to monitor these antibiotics. The frequent reports of gentamicin resistance among *E. coli*[19] and other gram-negative rods, and the number of infections due to the coagulase-negative staphylococci, many of which are resistant to gentamicin, have led to gentamicin being replaced by amikacin, kanamycin, or netilmicin in some units. Although these newer aminoglycosides may be less susceptible to enzymic degradation and may be more active against some organisms than gen-

tamicin, this is not always so. This was shown in the report of Lewis et al.[33]; in their neonatal unit, gentamicin was replaced by netilmicin because of increasing problems of resistance to gentamicin. Within 3 months, there was an outbreak of infection due to *Serratia marcescens*. Thirteen babies were affected; five were bacteremic and two died. The bacterial strain concerned was resistant to netilmicin, but it was sensitive to gentamicin. Faced with problems of gentamicin resistance among gram-negative rods, amikacin would appear to be the best alternative because it is resistant to more of the various degradation enzymes than the other available aminoglycosides. Netilmicin is the more active aminoglycoside against coagulase-negative staphylococci.[7] As reported above we have successfully used third-generation cephalosporins alone for blind therapy, and a few centers have found the ureidopenicillins also to be suitable.

The division of infection in the newborn into those of early- and late-onset was proposed with regard to the GBS infection. Some units have found it a useful division for bacterial infections as a whole. Early-onset infection is manifest during the first 48 hours of life and is a consequence of intrauterine or peripartum infection with bacteria from the mother's genital tract. Late-onset infection occurs after the second postnatal day and is usually a consequence of nosocomial transmission. In units where there is a clear distinction between the bacteria responsible for early- and late-onset infection it may be appropriate for the antibiotic regimens for blind treatment at these times to be different. Thus, ampicillin and gentamicin would be appropriate for the treatment of early-onset sepsis, on the basis that most mothers are admitted in labor from home and are therefore not colonized with hospital strains of *E. coli* and other gram-negative rods. In late-onset sepsis, where staphylococci are the most common bacteria involved, therapy with flucloxacillin and gentamicin, or possibly vancomycin, would be appropriate. In most units it is not possible to discern such a clear separation between the bacteria responsible for early and late sepsis, and as a result the regimen for blind therapy is directed toward the most frequent and significant bacteria associated with infection at the time. This may then be replaced with specific therapy once a microbe has been isolated. In general, nosocomial infection due to gram-positive organisms is less serious and less frequently fatal than is infection with gram-negative rods. Thus, initial therapy with a penicillin plus gentamicin or a third-generation cephalosporin will at least hold most infections until culture results are available and specific therapy can be instituted. In our unit during 1985, coagulase-negative staphylococci were isolated from 19 of 38 positive blood cultures. More of these staphylococci were sensitive to ceftazidime (the monotherapy in routine use at that time) than to gentamicin.

PROBLEM AREAS

Chloramphenicol is not frequently used in the treatment of neonatal sepsis in industrialized countries; however, because of its su-

perior penetration into CSF it has until recently remained the antibiotic of first choice in Great Britain for the treatment of neonates with suspected or proven meningitis. It is given alone or in combination with other antibiotics.[39] Despite the fact that the potential toxicity of chloramphenicol is well known, recent work has shown that overprescription and accidental overdosage are common.[38] Toxic side effects are associated primarily with serum concentrations persistently above the therapeutic range (15–25 mg per liter) and occur predominantly in the neonatal period. These arise from overdosing or inadequate monitoring. Our studies have shown that when chloramphenicol is administered correctly and is regularly monitored, problems of serious toxicity are rare.

In other countries, notably the United States, gentamicin is the antibiotic of choice for the treatment of meningitis in spite of its unreliable penetration into CSF. Attempts to increase CSF concentrations by intrathecal or intraventricular instillation of gentamicin have not improved the clinical response to this antibiotic, and this practice is not now recommended.[3-1] There is therefore a need for new, nontoxic and highly active compounds that will penetrate into the CSF in therapeutic concentrations. Third-generation cephalosporins have proved highly effective in the treatment of pediatric meningitis, and there are individual reports of their being used successfully in the newborn. To date there are no studies comparing traditional therapy with these agents in the treatment of meningitis in the newborn.

Changes in the bacteria responsible for neonatal conjunctivitis and ophthalmia neonatorum have necessitated a reassessment of the antibiotics used for routine therapy. In some countries penicillin can no longer be relied on for the treatment of gonococcal ophthalmia because of the high incidence of betalactamase-producing strains. Other Neisseria-like organisms causing ophthalmia, such as *Branhamella catarrhalis*, are also resistant to penicillin. In areas where infection with these organisms is common, the World Health Organization recommends intramuscular cefotaxime (100 mg per kg as a single injection) or intramuscular kanamycin (25 mg per kg) plus erythromycin (0.5 per cent) or tetracycline (1 per cent) eye ointment for 10 days. Where resistance is not common, gonococcal ophthalmia should be treated with aqueous crystalline benzylpenicillin intravenously (15 mg per kg every 12 hr) for 7 days. The eyes should be irrigated hourly with saline or buffered ophthalmic solution while the discharge persists.

Eye infections due to *Chlamydia trachomatis* may resemble gonococcal infection, except that they present during the second week of life. These infections require systemic treatment with erythromycin (12.5 mg per kg q 6 hr for 2–3 weeks) with or without the topical application of tetracyline ointment. This is necessary to eradicate nasopharyngeal carriage. Chloramphenicol, which is widely used to treat conjunctivitis in the newborn, will not cure chlamydial infection. The clinical condition may improve, but the organisms will persist. Prophylaxis against conjunctivitis in the newborn has been widely prac-

ticed since Crédé advocated the use of silver nitrate in 1881. This practice has been discontinued in the United Kingdom, although it is still used elsewhere. Silver nitrate has no effect on Chlamydia. Penicillin prophylaxis is to be discouraged because of the risk of provoking resistance. Tetracycline has been used prophylactically because it is also active against Chlamydia, but the evidence for its value is conflicting. The Centers for Disease Control recommend erythromycin as an alternative to silver nitrate in areas where the incidence of gonococcal and chlamydial infection is high. The most important aspect of preventing these infections in small babies is the diagnosis and treatment of their mothers before delivery.

Necrotizing enterocolitis remains a recurrent problem in many premature infant care units. The role of bacteria in its etiology remains far from clear; although antibiotics are invariably prescribed, their efficacy, other than in the treatment of an accompanying bacteremia, has not been established. Various antibiotic regimens are currently in use. A combination of penicillin, gentamicin, and metronidazole is probably used most widely; but penicillin plus gentamicin, cephalosporin plus gentamicin, and vancomycin alone all have found favor. Some units simply use an antibiotic "cocktail" different from that which the babies received previously. Until there is a breakthrough in our knowledge about the etiology of necrotizing enterocolitis, it is difficult to be certain about the role of antibiotics in its management or the correct regimen to use.

The dramatic increase in neonatal infections due to *Staphylococcus epidermidis*[18] and the fact that many strains isolated are resistant to gentamicin or methicillin have led to an increase in the use of vancomycin during the newborn period. Vancomycin has a unique mode of action against sensitive bacteria; its primary action is to inhibit bacterial cell wall synthesis, but in addition it alters cell membrane permeability and there is evidence that it also inhibits the synthesis of nucleic acid. As a result of this multiple effect on susceptible bacteria, resistant strains are rarely encountered. Vancomycin is highly active against *Staphylococcus aureus*, including methicillin-resistant strains, and most strains of *Staphylococcus epidermidis*. The combination of vancomycin and rifampicin has been reported to be synergistic against *Staphylococcus epidermidis*, but it is antagonistic or has an indifferent effect against *Staphylococcus aureus*.

Currently recommended dosage regimens for vancomycin of 30 to 40 mg per kg per day frequently produce a serum concentration above the recommended therapeutic range (TR peak 20–30 mg per liter serum—trough < 12 mg per liter). Levels above 50 mg per liter are considered to be potentially toxic.[1] Because of this there is the need for routine assay of this antibiotic (discussed later). Current formulations are far less likely to result in toxic effects than those used previously. However, renal toxicity is increased if vancomycin and gentamicin are given together. Vancomycin is associated also with ototoxicity in the newborn, but there is little information on this subject. It is apparent from the report of Odio et al.[42] that the toxic effects

of vancomycin may be increased in patients who recently have been anesthetized. This may be significant for babies undergoing surgical operations. Many of the adverse effects from vancomycin can be eliminated by increasing the infusion time for each dose from 30 to 60 minutes.

Some workers propose that the "peak" sample should be taken 30 to 60 minutes after the end of the infusion. Although there are clear advantages to this approach, toxicity and efficacy data have not been determined on the basis of "peak" samples collected at this time. Acceptable serum concentrations 30 to 60 minutes after the end of infusion would be 20 to 30 mg per liter compared to levels up to 50 mg per liter proposed by Schaad et al. for samples collected immediately after the infusion is finished. All workers agree that repeated assay of vancomycin is essential in small babies to ensure therapeutic efficacy without toxicity.

EVALUATION

The evaluation of new antimicrobial agents in the treatment of neonatal infection is difficult. Comparative randomized controlled trials between an established antibiotic regimen and a new compound have not been carried out. If the standard regimen is highly effective, very large numbers of babies would be needed to establish the therapeutic superiority of a new regimen, especially where the prevalence of infection is low. If the standard regimen has ceased to be effective, then a randomized comparative trial would be unethical. The less satisfactory alternative is to use open studies to establish that the new therapeutic regimen is at least as effective as that used previously for the treatment of clearly defined neonatal sepsis and then to determine whether a diminished risk of toxicity, more desirable pharmacokinetics, more convenient dosage regimens, and so forth, give the new agent significant advantage over the old. This has been used most effectively to compare traditional aminoglycosides or chloramphenicol-based regimens with the new cephalosporins for the treatment of pediatric meningitis. In our practice, the approach has been to use matched populations to evaluate alternatives to the aminoglycosides for the treatment of neonatal sepsis.

THIRD-GENERATION CEPHALOSPORINS

The introduction of the third-generation cephalosporins, the ureidopenicillins, and the oxo-betalactam antibiotic moxalactam (Latamoxef) into neonatal practice has provided pediatricians with a wider choice of safe, highly active antimicrobial agents then ever before. In addition to the extraordinary activity of these agents against gram-negative enteric rods, including strains resistant to gentamicin, they

are highly active also against many other neonatal pathogens. Unlike the earlier cephalosporins, these agents achieve high concentrations in the CSF of patients with meningitis. There is evidence also that during the first 2 weeks of life the third-generation cephalosporins, cefotaxime, ceftazidime, and ceftriaxone penetrate into the CSF in therapeutic concentrations in the absence of meningeal inflammation (de Louvois J: Unpublished information, 1985). All of these agents are safe when used at the recommended dosage and do not carry the risk of ototoxicity or renal toxicity associated with the aminoglycosides. They also have predictable pharmacokinetics, and because the difference between therapeutic and toxic serum concentrations is so wide, they do not require routine monitoring.

These compounds, however, are not totally free from drawbacks. As a group the cephalosporins are not only inactive against *Listeria monocytogenes* but also against enterococci. Babies treated with these agents may become heavily colonized with enterococci. Only on rare occasions do enterococci cause primary infection in the newborn, and suprainfection with these organisms following cephalosporin therapy is rare. Moxalactam is ineffective against group B streptococci and should not be used alone until the possibility of infection with this organism has been excluded. Of the new betalactam antibiotics available, only piperacillin and ceftazidime are clinically active against *Pseudomonas aeruginosa*. The newer cephalosporins are less active than their predecessors against staphylococci; however, because of the high serum levels achieved, staphylococcal infections have been successfully treated with these agents.[24, 26] These workers have observed also that strains of *Staphylococcus epidermidis* isolated from the blood of bacteremic neonates are more often resistant to gentamicin than to cefotaxime.

Ceftriaxone and moxalactam achieve high concentrations in the bile, which leads to a reduction in bowel flora.[52]

NEW ANTIBIOTICS

The introduction of the third-generation cephalosporins has permitted a reassessment of the most appropriate therapy for bacterial infections in the newborn. It seems probable that they will soon replace chloramphenicol- and aminoglycoside-based regimens for the treatment of meningitis and in other areas also they are proving effective. Augmentin and similar combinations of a betalactam antibiotic and a betalactamase inhibitor, such as clavulanic acid, have not been used extensively in the newborn. Looking to the future, aztreonam and the thienamycins have high activity against many neonatal pathogens and are unlikely to prove toxic. In contrast, the quinolone group of antibiotics is unlikely to be used routinely in neonatal practice because of concern about possible side effects.

ANTIBIOTIC DOSAGE

The recommended dosages for antibiotics used in the treatment of the newborn are shown in Table 5. Toxic antibiotics, aminoglycosides, chloramphenicol, and vancomycin should be assayed every 48 hours during the neonatal period, and the dosage or dosage interval modified to maintain serum concentration within the therapeutic range. In our experience, a 12-hour dosage interval is more appropriate for chloramphenicol than one of 6 hours. In premature babies receiving gentamicin, we give three quarters of the daily dose (i.e., 3.8 mg per kg) every 18 hours in preference to a dosage of 2.5 mg per kg every 12 hours. This ensures that the preinjection serum concentration is 2 mg per liter or less while at the same time giving a therapeutic peak concentration.

ROUTE OF ADMINISTRATION

Most antibiotics may be administered equally effectively to neonates by either the intravenous or intramuscular route.[37] The exception is chloramphenicol, which shows poor absorption following intramuscular administration. In the newborn, oral administration of chloramphenicol also results in poor absorption and the oral route should not be used.[40] This is in contrast to its use in older children, to whom chloramphenicol is given by mouth as soon as the child is able to swallow. Except for ampicillin and flucloxacillin, there is little information on the oral absorption of other antibiotics in the newborn; because of this and the risk of regurgitation and aspiration, the oral route cannot be recommended for small babies. In the future it may prove possible to administer antibiotics transdermally to babies younger than 28 weeks' gestation.

DURATION OF TREATMENT

Treatment of neonates receiving antibiotics for clinical signs of sepsis should be reassessed after 48 hours, when the results of pretreatment bacteriologic cultures are known. At that time, the clinical condition of many of those treated will have improved dramatically, and if bacteriologic cultures are negative, antibiotic therapy may be stopped. Babies who continue to show clinical signs of infection should be treated for at least 5 days, whether pathogenic bacteria have been isolated or not. If chemotherapy is to continue for longer than 5 days, the septic screen should be repeated to determine whether suprainfection or colonization with resistant bacteria has occurred, in which case a change of therapy usually is required. Although a 5-day course of treatment is sufficient for the treatment of many established infections, a longer course may sometimes be required. Treatment of

Table 5. *Recommended Dosage of Antibiotics for Use in the Newborn*

DRUG	ROUTE	PREMATURE INFANTS AND TERM INFANTS LESS THAN SEVEN DAYS (MG/KG/DAY)	TERM INFANTS MORE THAN SEVEN DAYS (MG/KG/DAY)
Penicillin	IV, IM	30–45 (Div 12 hrly)	45–60 (Div 8 hrly)
Ampicillin	IV, IM	100 (Div 12 hrly)	150 (Div 8 hrly)
Carbenicillin	IV, IM	300 (Div 8 hrly)	400 (Div 6 hrly)
Ticarcillin	IV, IM	225 (Div 8 hrly)	300 (Div 6 hrly)
Piperacillin	IV, IM	200 (Div 12 hrly)	200 (Div 12 hrly)
Chloramphenicol*	IV	25 (Div 12 hrly)	37.5–50 (Div 12 hrly)
Gentamicin*	IV, IM	5 (Div 18 hrly)	5 (Div 12 hrly)
Netilmicin*	IV, IM	5 (Div 12 hrly)	5 (Div 12 hrly)
Tobramycin*	IV, IM	4 (Div 12 hrly)	6 (Div 8 hrly)
Cefotaxime	IV, IM	100 (Div 12 hrly)	100 (Div 12 hrly)
Ceftazidime	IV, IM	100 (Div 12 hrly)	150 (Div 8 hrly)
Moxalactam	IV, IM	100 (Div 12 hrly)	150 (Div 8 hrly)
Erythromycin	IV (slow)	40–60 (Div 6 hrly)	40–60 (Div 6 hrly)
Vancomycin*	IV as 60-min infusion	30 (Div 12 hrly)	30 (Div 12 hrly)
Rifampicin	IV	10 (Div 12 hrly)	10 (Div 12 hrly)
Metronidazole	IV	20 (Div 8 hrly)	20 (Div 8 hrly)

* Antibiotics to be assayed routinely.

bacterial pneumonia should continue at least until the x-ray picture has returned to normal. In the treatment of necrotizing enterocolitis, chemotherapy is continued until 5 days after the disappearance of intramural gas or the last blood-stained stool. Bacterial meningitis requires 2 to 3 weeks of chemotherapy; treatment must be given parenterally because of the risk of ventriculitis and recurrent infection.

MONITORING OF THERAPY

The wide inter- and intrapatient variation in drug pharmacokinetics that has been reported during the neonatal period, coupled with the paucity of data on babies of less than 28 weeks' gestation means that very few assumptions can be made about use of antibiotics in the newborn. As a result, it is necessary to monitor antibiotic concentrations not only for the potentially toxic compounds but occasionally also to ensure that therapeutic concentrations are being achieved. Great publicity has been given to the potential toxicity of the aminoglycosides and a wide range of expensive equipment has been developed for measuring serum concentrations of these compounds. It is apparent from recent reports that the aminoglycosides are not as toxic to newborn babies as was previously feared. In addition to the medicolegal considerations, which will ensure that aminoglycoside assays remain a routine investigation, there is the clinical need to know how these drugs are handled by individual babies receiving treatment. On the strength of assay results, dosage intervals and regimens may need to be changed frequently to maintain serum concentrations within what is considered to be the safe therapeutic range; that is, a peak concentration of less than 10 mg per liter, and a trough concentration of less than 2 mg per liter. Simple measurement of serum concentrations, however, does nothing to identify the problem of toxic drug concentrations (e.g., the increased renal toxicity associated with the combination of gentamicin with cephaloridine). Although there is apparently little risk of aminoglycoside association toxicity in the newborn when standard dosage regimens are adhered to, the same cannot be said for chloramphenicol. Recent studies[38] have shown an alarming level of serious toxic effects from this antibiotic, leading in some cases to death. Although some of these effects can be accounted for by overprescription or an accidental overdose, serious toxic side effects can occur following appropriate dosage and administration of chloramphenicol. It is therefore essential that serum concentrations are regularly determined in all babies receiving this antibiotic. This may be done most effectively using high-performance liquid chromatography (HPLC), which also will determine levels of unhydrolyzed ester, but there are quick and easy microbiologic methods.[21] Peak serum concentrations of chloramphenicol should not exceed 25 mg per liter, and trough concentrations should be in the range of 12 to 15 mg per liter. Idiosyncratic variation is found also with vancomycin, and, although vancomycin-associated neonatal deaths have not been reported re-

cently, this drug should be assayed routinely. Therapeutic serum concentrations for vancomycin should be in the range of 20 to 50 mg per liter. Other antimicrobial drugs that should be assayed routinely include rifampicin and amphotericin B.

TOXICITY

The toxic effects of the tetracyclines on the fetus and newborn baby are well established, and these antibiotics should not be used systemically in pregnant women or in children except when there are very special indications, such as Mycoplasma meningitis. Infrequent minor changes to eighth nerve function have been reported in children exposed to streptomycin during intrauterine life, but not in those whose mothers received kanamycin in pregnancy. The safety of gentamicin and netilmicin during pregnancy has not been established, and there are no figures on the incidence of toxic side effects due to either antibiotic.

Although chloramphenicol therapy during pregnancy may produce toxic side effects in the mother, there is no evidence that any adverse effect is produced in the fetus. Treatment late in pregnancy is accompanied by a theoretic risk of toxic manifestations in the newborn, but such toxicity has never been reported.

The toxicity of the penicillins and cephalosporins in the neonate is exceptionally low. Babies born to mothers who are hypersensitive to penicillin may show similar hypersensitivity, and it is wise to avoid penicillin or ampicillin therapy. Most of these babies will not react if given cephalosporins.[48] Very rarely, hemolytic anemia develops following treatment with penicillin and rather more frequently following administration of cephalothin. Treatment with cephalothin and, to a lesser extent, other penicillins and cephalosporins may result in a false-positive Coombs's test result. Cephalosporins possessing the N-methylthiotetrazole moiety (e.g., cephamandole, cefoperazone, moxalactam) may elicit a disulfiram-like reaction, with a widespread erythematous rash in babies who also are receiving alcohol-based medication (e.g., we have seen it with phenobarbitone elixir).

Some of the early cephalosporins (notably cephalothin, cephaloridine, and cephazolin) were potentially nephrotoxic; this side effect was increased dramatically if they were administered in combination with an aminoglycoside. The newer cephalosporins are thought to be much safer in this respect, and cefotaxime or ceftazidime can be safely administered with gentamicin to treat life-threatening infections. Attempts to reduce the concentration of aminoglycosides or chloramphenicol by exchange transfusion, peritoneal dialysis, hemodialysis, or chemical removal have proved unsuccessful and hazardous. As a result, if potentially toxic concentrations of antibiotic are found in a neonate, no positive intervention should be attempted other than to maintain good renal function. The antibiotic should be discontinued

until serum levels return to the therapeutic range. In extreme cases this may take 6 or 7 days.

ADVERSE EFFECTS OF ANTIBIOTIC THERAPY

The usefulness of an antibiotic may be related directly to the speed with which resistance develops among previously sensitive organisms. The single-step resistance observed with streptomycin has not been found with subsequent aminoglycosides. Although gentamicin has been used extensively in neonatal practice for many years, it is only recently that problems with resistance have been reported. In contrast, among sensitive strains of *Pseudomonas aeruginosa* resistance to carbenicillin appeared very soon after the antibiotic was introduced; 50 per cent strains may now be expected to be resistant to this antibiotic. The high risk of resistance developing during treatment limits the use of antibiotics such as fusidic acid. In an attempt to prevent this, it is often recommended that fusidic acid should be combined with another antistaphylococcal antibiotic, although the evidence that this is effective in preventing resistance is limited. It remains to be seen to what extent development of resistance will be a problem with the new antibiotics. Of greater concern with the broad-spectrum antibiotics is overgrowth with inherently resistant organisms. In our experience, the rate of colonization with yeasts is no higher after therapy with the cephalosporins than it was after gentamicin and ampicillin. We have, however, observed increased colonization with fecal streptococci as a consequence of cephalosporin therapy. These organisms have not caused serious problems; nevertheless, it is our practice to add oral ampicillin if a cephalosporin regimen is to continue for more than 5 days or if the baby is more than a week old when treatment starts. Whatever antibiotic regimen is employed, it is essential that a close watch is kept on the sensitivities of organisms isolated from the neonatal unit so that resistant strains may be recognized before they cause problems. The indiscriminate use of topical antibiotics greatly increases the speed with which resistant bacterial strains appear, and this also increases the risk of antibiotic sensitization. In addition, toxic antibiotics, such as neomycin, applied to skin surfaces may be absorbed in sufficient concentration to produce deafness in preterm babies.[36]

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Pulmonary Hypertension and Persistent Fetal Circulation in the Newborn

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Persistent pulmonary hypertension of the newborn (PPHN) is one of the most challenging clinical syndromes commonly seen in the neonatal nursery. Over the past decade, there have been several exciting advances in the care of these infants. This article will review the current understanding of factors controlling pulmonary hypertension, development of a more specific prognostic score, changes in clinical care, description of a new form of ventilation, and advances in followup care.

An important realization is that infants with a wide variety of underlying clinical conditions develop PPHN. It is likely that the specific factors mediating the pulmonary artery hypertension are different in each of the groups of infants, depending on the clinical condition and its etiology. Infants with group B streptococcal sepsis and pulmonary artery hypertension are one such subgroup, and the mechanism underlying the hypertension has been suggested by recent work with an animal model of PPHN. In this model, an infusion of group B streptococci is used to produce a rise in pulmonary artery pressure (PAP). The rise in the PAP is proportional to the rate of intravenous infusion.[54] Using this model, investigators have suggested that thromboxane A_2 may be an important mediator of pulmonary artery hypertension, and pretreatment with indomethacin markedly reduced the acute rise in PAP in the animal model.[56, 57]

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A different etiology of pulmonary hypertension may be present in infants with meconium aspiration syndrome. This syndrome is one of the clinical conditions most commonly associated with pulmonary artery hypertension.[25] In the meconium aspiration syndrome, many of the pathophysiologic changes involve alterations in lung mechanics, leading to air trapping and a chemical pneumonitis. It is possible that a combination of vasoactive substances and mechanical forces may mediate PAP in these infants.

Two types of anatomic changes in lung development indicate additional subgroups of infants with pulmonary artery hypertension. Anatomic work has suggested that infants with PPHN show both hypertrophy of the pulmonary arterial musculature and an extension of the muscular development in the pulmonary arterioles closer to the alveolar–capillary unit when compared to normal.[44, 48] The other example of anatomic changes associated with PPHN is the syndrome of either severe or moderate pulmonary hypoplasia. Infants with diaphragmatic hernia fall into this category. These babies demonstrate a wide spectrum of disease severity, ranging from those with minimal hypoplasia and mild pulmonary vascular hyperreactivity to those with severe pulmonary hypoplasia and severe fixed pulmonary artery hypertension, who are unresponsive to any of the current modes of intervention. Given the wide variety of clinical conditions that can be associated with pulmonary hypertension, it is not surprising that reports of survival vary widely. The extensive range of survival reported in different series emphasizes the need for more precise definition of underlying disease states and disease severity.

CURRENT KNOWLEDGE OF THE PATHOPHYSIOLOGY OF PPHN

PPHN is not a distinct disease, but rather an example of the fetal circulation that has not made an adequate transition to a normal neonatal circulation. The entire clinical picture of PPHN—high pulmonary artery pressures, low pulmonary blood flow, and massive right-to-left shunting at the foramen and ductal levels, causing profound hypoxemia minimally responsive to supplemental oxygen—is a reflection of the persistently high pulmonary vascular resistance that ensues when the transitional circulation does not proceed normally. Any stimulus that causes failure of the transitional circulation will cause the clinical syndrome of PPHN. Over the past decade, significant progress has been made in the understanding of the complex processes that compose the normal transitional circulation.

The result of the transition is to take the *in utero* physiology of high pulmonary vascular resistance (PVR) and functionally parallel ventricular output to that of the postnatal state of relatively low PVR and series ventricular output. Indeed, the transition is virtually synonymous with PVR reduction. As stated above, if the PVR does not diminish in the usual manner or to the usual extent, the clinical picture

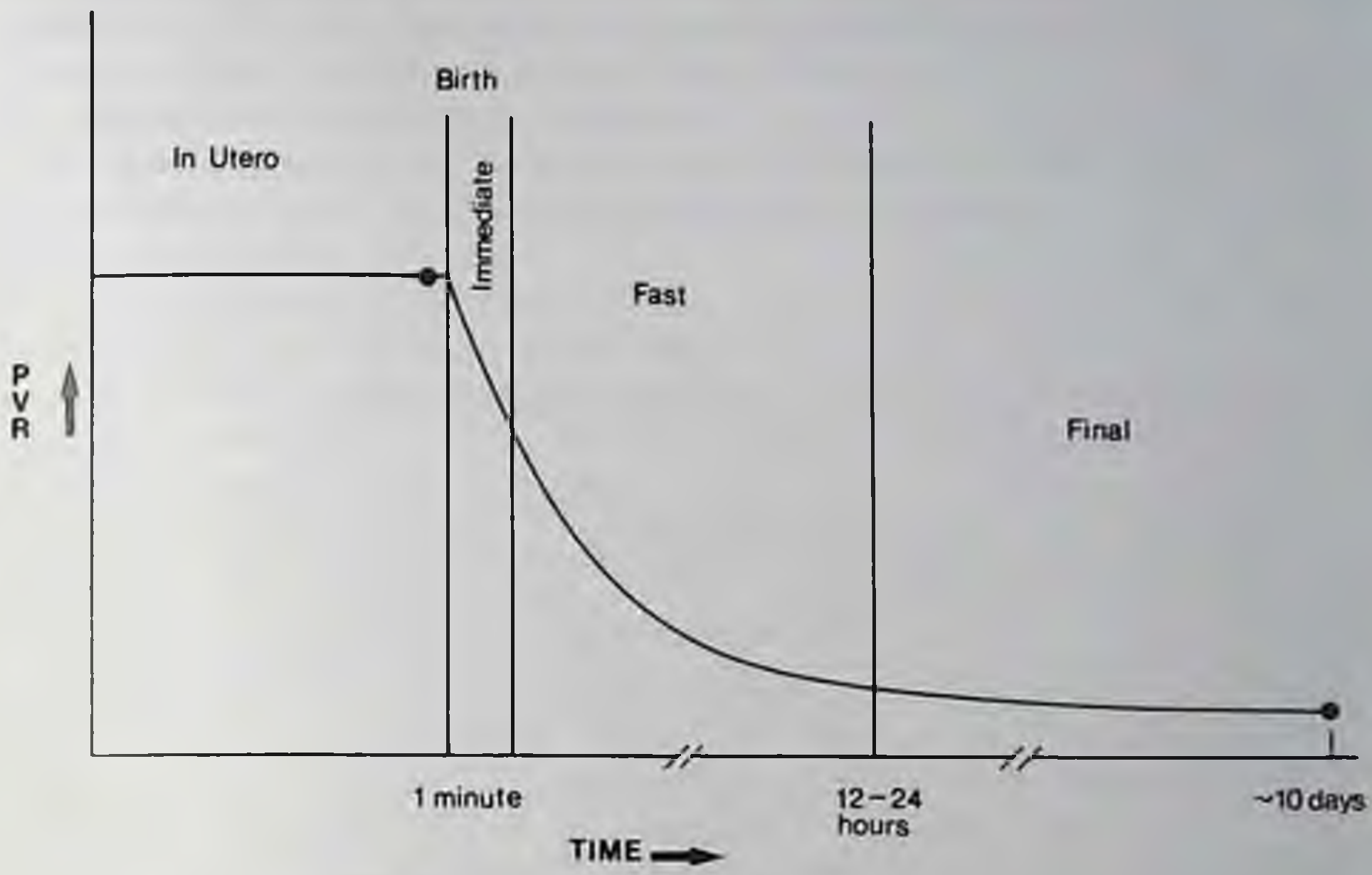

Figure 1. The four phases of transitional circulation.

is that of PPHN; the clinical magnitude of the PPHN varies inversely with the degree of PVR reduction. Understanding the processes that control the PVR *in utero* and during the transition provides information on the pathophysiology and treatment of PPHN. Four areas of research that seem particularly promising are discussed: the time course of the transitional circulation, the role of prostacyclin, the role of leukotrienes and thromoboxanes, and the role of oxygen.

THE TIME COURSE OF THE TRANSITIONAL CIRCULATION

Although it has been known for some years that closure of the ductus even in the term infant may not be complete for days and that the final reduction in PVR takes a matter of weeks, the general concept remains that a neonate has two states: before the transition and after the transition. Recent evidence has made it clear that the transitional circulation is not an event but a process that occurs in distinct phases: an *in utero* phase, an immediate phase, a fast phase, and a final phase. These phases and their relative time courses are shown schematically in Figure 1. A full description of the phases of the transitional circulation and their defining characteristics has recently been presented.[13] This concept of the transition being divided into distinct phases with very different physiologic and pharmacologic properties probably explains the ability of a given stimulus (e.g., asphyxia or sepsis) to induce a failure of normal PVR reduction, and thus cause

PPHN, at one point in the transitional circulation and not another. At present, one cause of PPHN (that induced by cyclo-oxygenase inhibitors) seems clearly associated with the failure of a particular phase of the transitional circulation. However, it is important to begin to think of the neonate as having three states—before, during, and after the transition—and being at variable risk for PPHN from a given insult in each of these states.

THE ROLE OF PROSTACYCLIN

Figure 1 shows that the fast phase of the transitional circulation is that phase when most of the PVR reduction occurs. The distinctive characteristics of the fast phase is the sudden and massive production of pulmonary prostacyclin.[35–37] Prostacyclin, one of the naturally occurring products of the cyclo-oxygenase pathway, is a powerful vasodilator. In mature animals, pulmonary prostacyclin is known to act as a modulator of the pulmonary artery pressure. Pulmonary prostacyclin production increases whenever the pulmonary artery pressure is increased, with the result that the raised pressure is regulated downward.[19, 28, 66] This same mechanism is used to reduce the "elevated" pulmonary artery pressure that characterizes the early period of the transitional circulation. Leffler and co-workers have demonstrated that the initiation of ventilation (i.e., the immediate phase) causes the production of large amounts of endogenous prostacyclin from neonatal lungs, and this prostacyclin production is associated with the reduction of PVR.[37] Pretreatment of the fetus with indomethacin, which inhibits prostacyclin production by blocking the enzyme cyclo-oxygenase, prevents the reduction in PVR that occurs after the initiation of ventilation. These findings may have profound clinical implications. There have been several reports of infants with PPHN born to mothers who had received drugs such as aspirin or nonsteroidal anti-inflammatories (NSAIDs), all of which block cyclo-oxygenase. Sufficient doses of these drugs given to the mother might transfer across the placenta to the fetus and cause failure of the transitional circulation by inhibiting pulmonary prostacyclin production. With the renewed interest in using NSAIDs as tocolytics, it is possible that infants born in spite of this form of tocolysis may exhibit PPHN due to the failure of the prostacyclin-dependent fast phase of the transitional circulation.[30, 65]

THE MEDIATORS OF THE FETAL PVR

The clinical conditions or insults associated with PPHN may result from some combination of two mechanisms: causing a failure to initiate the systems that actively reduce PVR, such as was described in the previous section or causing those systems that maintain high PVR *in utero* to persist after the initiation of ventilation. The mech-

anisms responsible for the high PVR *in utero* are currently active areas of research by several groups. These are rapidly emerging stories, and much of the data to be presented await confirmation. With that caveat in mind, however, it appears that leukotrienes and hypoxic pulmonary vasoconstriction (HPV) represent the best current candidates for these mechanisms and for directions for research into the pathophysiology and treatment of PPHN.

It is unlikely that prostaglandins play a physiologic role in maintaining the high PVR *in utero* since fetal lungs are known to be net catabolizers of prostaglandins until the initiation of ventilation and the beginning of the fast phase of the transitional circulation. This is not the case for other eicosinoids, however. Recently, particular interest has been focused on the possible role that the leukotrienes and thromboxanes may play in both the normal and pathologic physiology of the fetal pulmonary circulation. Saeed and Mitchell[58] have provided data indicating that lipoxygenase (the enzyme that produces the leukotrienes from arachidonic acid) is present in human fetal lungs by 12 to 18 weeks' gestation. Data from several laboratories have indicated that the leukotrienes might be crucial to the pulmonary vasoconstrictive response to hypoxia.[40, 46] Inhibition of either leukotriene synthesis or action blocks the hypoxic pressor response. This line of research has been complemented by the report of Stenmark of elevated levels of some leukotrienes (LTC_4 and LTD_4) in the lung lavage of infants with PPHN.[64] At this point, however, the story becomes less clear but more exciting. Several workers have demonstrated that exogenous leukotrienes can elevate the PVR in fetal animals and that these effects can be blocked by the putative leukotriene receptor antagonist FPL 55712. Another putative leukotriene blocker, FPL 57231, has been shown to increase pulmonary blood flow dramatically when injected into fetal lambs, the effect that would be anticipated if leukotrienes were causing the high PVR of the fetus. If these observations prove to be true, combined with the data from Stenmark, they provide exciting possibilities for very specific therapy for PPHN in selected infants. Unfortunately, an increasing amount of data suggests that these FPL substances, as well as other compounds that were previously thought to be lipoxygenase inhibitors, may not be specific but possess a vast range of pharmacologic effects. Thus, the relationship of the leukotrienes to the regulation of normal and pathologic transitional circulation remains an area of great potential for further research. An excellent review article by Cassin summarizes the state of knowledge concerning the role of eicosinoids in the control of the transitional circulation as of late 1986.[11]

THE POSSIBLE ROLE OF OXYGEN AND HYPOXIC PULMONARY VASOCONSTRICTION IN THE CONTROL OF THE TRANSITIONAL CIRCULATION

Finally, one emerging line of research holds potential for not only explaining aspects of the basic physiology of the transitional circu-

lation but also elucidating the mechanism behind some of the more successful therapies for PPHN. It has been known for over three decades that there is marked streaming of blood in the heart *in utero*, with the lungs receiving the intensely desaturated blood returning from the head. The Po_2 of the blood actually entering the lungs *in utero* is approximately 17 mm Hg. In the adult animal, mixed venous blood with such a low Po_2 is a stimulus to hypoxic pulmonary vasoconstriction[42] even when there is 21 per cent Fio_2 in the alveoli since it has been established that HPV is a function of both the Po_2 in the mixed venous blood and in the alveoli. In the fetus, the Po_2 of the fluid-filled alveoli is in equilibrium with the low Po_2 of the blood, presenting a very powerful stimulus for HPV. This raises the interesting question as to whether the high PVR *in utero* is a reflection of HPV. Teleologically, this is an especially appealing concept on two counts. First, it would explain the high *in utero* PVR by means of a physiologic mechanism that is active throughout life and not require the invocation of a mechanism that is active only during the perinatal period. Second, it presents a mechanism for the regulation of perinatal PVR that has exactly the type of negative feedback that is required of the transitional circulation. Therefore, once the process of "turning off" the high PVR is begun, each successive reduction in the PVR further reduces the stimulus for HPV, and the cycle thus continues, reinforcing itself, until the PVR is substantially reduced.

Before the first breath, the lungs are airless and are receiving only a small amount (about 8 per cent of the combined cardiac output. With the first breath two events occur. First, the vasculature of the pulmonary bed is "pulled" open, reducing the PVR through purely mechanical means (this is the immediate phase of the transitional circulation). This reduction of the PVR allows not only more blood to enter the lungs, but better oxygenated blood, as now blood that has returned from the placenta tends to enter the right ventricle and thus the lungs in greater quantity. In addition, the entry of air into the lungs suddenly increases the Po_2 in those alveoli that are expanded (by no means the majority) from 17 to well over 100. The combined effect of these two events is a dramatic reduction in the stimulus to HPV.

An important negative aspect of this process must be pointed out, however. If for some reason the Po_2 in either the alveoli or the mixed venous blood falls, then exactly the opposite cycle will ensue. A slight rise in PVR will cause right-to-left shunting of blood. Further desaturation of the returning mixed venous blood then occurs, leading to the onset of a vicious downward cycle. Anyone who has cared for infants with PPHN will recognize in this scenario a description of the tremendous lability in systemic arterial saturation that these infants manifest. Finally, it is interesting to note that current therapies for PPHN might be explained by these HPV effects in the transitional circulation.

From the foregoing discussion, it becomes clear why ventilation with high Fio_2 and when clinical improvement occurs, extraordinarily

slow reductions in Fio_2 are indicated. Likewise it is clear that paralysis, sedation, and minimalization of such activities as manipulation and suctioning, all of which reduce sudden increases in intrathoracic pressure, which in turn reduce pulmonary blood, are clinically useful. What is less clear is why lowering the Pco_2 might be helpful. However, recent data by Marshall[41] have shown that in isolated, perfused lungs the pulmonary pressor response to hypoxia (i.e., HPV) is diminished with either respiratory or metabolic acidosis. Thus, if some cases of PPHN represent HPV gone awry, raising the pH may prove efficacious in lowering the PVR.

Recent experimental evidence indicates that hypoxic pulmonary vasoconstriction may play a role in the control of the transitional circulation as well as in conditions *in utero*. Morin and colleagues[47] have presented preliminary data indicating the pulmonary blood flow of fetal lambs *in utero* can be substantially raised by placing the ewes in hyperbaric oxygen and increasing the fetal mixed venous Po_2 to approximately 55 mm Hg. Ongoing work indicates that in exteriorized fetal lambs in which the lungs are pump perfused by blood from a bubble oxygenator, the PVR falls as the Po_2 of the perfusing blood is increased.

In summary, the pathophysiology of PPHN must be viewed from the perspective of a failure of some portion of the transitional circulation. While the physiology of the transitional circulation is not fully understood at present, it is clear that there are several interacting mechanisms that occur over the process of the transition and bring about the reduction of the pulmonary vascular resistance. The failure of one or more of these mechanisms will lead to the inability to reduce PVR in the normal manner and thus the clinical picture of PPHN. As more is understood about the physiology of the normal transitional circulation, no doubt our understanding of the various pathophysiologies that lead to PPHN will improve.

PREDICTING SURVIVAL IN INFANTS WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Despite current therapeutic modalities, mortality rates in infants with PPHN still approach 40 per cent.[2] As stated previously, the clinical outcome is variable because PPHN is associated with so many separate clinical entities.[23] Recently, extracorporeal membrane oxygenation (ECMO) and high-frequency ventilation (HFV) have been reported to be an effective treatment in some of these critically ill infants. However, difficulty with study design and patient selection criteria make many of these ECMO studies difficult to interpret. It would be most advantageous to identify those infants at higher risk for adverse outcomes as early as possible (within the first 24 hours) in the course of their disease so that infants with the poorest prognosis could be referred with relative safety to centers with ECMO or HFV capability. It would also be advantageous to identify infants who will

Table 1. *Scoring System to Predict Survivors of Persistent Pulmonary Hypertension of the Newborn*

SCORE	0	1	2
Maximum ventilator frequency (breaths per min)	>100	60–100	<60
Critical $PaCO_2$ (mm Hg)	<20	20–30	>30
Maximum peak inspiratory pressure (mm Hg)	>35	25–35	<25
Lowest pH	<7.10	7.10–7.25	>7.25
Apgar score (5 min)	<4	4–6	>6

survive with conventional treatment only and so obviate the need for transfer to those tertiary centers.

To define specific criteria that would assist in determining prognosis in infants with PPHN, 55 infants were evaluated retrospectively at two major medical centers from 1983 to 1986.[15] A diagnosis of PPHN was made by contrast echocardiography, cardiac catheterization, pre- and postductal arterial oxygen gradients, and by positive hyperoxic-hyperventilation testing. PPHN was associated with meconium aspiration, asphyxia, sepsis, and congenital diaphragmatic hernia in these infants. Premature infants were excluded. Infants were treated with hyperventilation, fluids, pressors, antibiotics, and vasodilators, depending on the clinical status of each patient.

Of the 55 infants studies, 35 infants survived (66 per cent). The mean BW ± SD was 3.34 ± 0.57 kg and the GA was 39.7 ± 1.5 weeks. Twenty infants died (34 per cent, 2 to 9 days after birth. Compared to surviving infants, the BW was 3.58 ± 0.56 kg ($p = NS$) and the GA was 41.0 ± 1.5 weeks ($p \leq 0.005$). A multivariate discriminant analysis of risk factors was performed comparing the group of infants who survived with the infants who died. Among a variety of perinatal and neonatal risk factors analyzed, maximal ventilator frequency, critical $PaCO_2$, maximal peak inspiratory pressures (PIP), lowest pH, and the 5-minute Apgar score were found by Student t-test to be significantly different between these two groups within the first 24 hours of life. A scoring system was developed to estimate prognosis based on these five criteria as shown in Table 1. Mean total score for surviving infants was 6.3 ± 1.3, whereas infants who died scored 2.7 ± 1.7 ($p < 0.0001$). Seventeen of eighteen infants (94 per cent) scoring ≤4 died. The one remaining infant developed severe bronchopulmonary dysplasia (BPD) as a sequela of the illness and treatment. All infants ($n = 13$) scoring ≥7 survived. Of 24 infants scoring 5 or 6, 21 survived.

To confirm these results, a logistic regression analysis was performed. Lowest pH, critical $PaCO_2$, and highest PIP were chosen by the logistic regression as the most important variables by a stepwise fitting process that began with all five variables used in the clinical scoring system. The logistic regression analysis predicted outcome perfectly, being negative with all deaths and positive in all survivors.

These results suggest that this clinical scoring system, when performed within the first 24 hours of life, is highly predictive of outcome in infants with PPHN. Currently, ECMO and HFV are being viewed as life-saving techniques in the treatment of PPHN. Boynton et al. suggest that HFV may facilitate adequate gas exchange at lower inspiratory pressures in critically ill infants with PPHN.[9] Kohelet et al. suggest that early initiation of HFV in infants with PPHN may improve survival and reduce the incidence of BPD that develops in the survivors.[33]

Bartlett et al. report 100 per cent survival in 10 infants with PPHN treated with ECMO.[2] However, ECMO therapy is not without significant risks. These include an increased incidence of cerebral infarction in infants treated with ECMO, presumably from ligation of the common carotid artery and internal jugular vein.[61] In addition, intracranial and other types of hemorrhage may occur secondary to anticoagulant therapy that is necessary while infants are on ECMO.[45] Therefore, it should be considered only in infants who have failed maximal medical therapy and have the poorest prognosis. Bartlett's study of ECMO has been criticized because of randomization techniques[50] and entry criteria used. A Newborn Pulmonary Insufficiency Index equal to a mortality rate of ≥80 per cent at 24 hours was one of the criteria used to justify entry into the study.[2] However, Kirkpatrick et al. suggest that hyperventilation therapy increases pH and makes the Newborn Pulmonary Insufficiency Index invalid as an appropriate entry criterion.[32] Dworetz et al. studied nine infants weighing more than 2 kg with PPHN in 1986 and found that six infants met appropriate ECMO entry criteria used by Bartlett.[18] These infants were then managed conservatively (without hyperventilation therapy), and 83 per cent survived, suggesting that criteria for ECMO need to be revised based on the improved survival that may be obtained using current medical therapies.

There are reports in the literature attempting to predict mortality accurately in infants with PPHN. In 1973, Raphaely and Downes evaluated infants with congenital diaphragmatic hernias before and after surgical repair.[53] Infants with preoperative (A–a)Do_2 gradients >500 mm Hg did not survive. This study, however, occurred before current medical therapies for treating these infants became available. In 1984, Krummel et al. found that (A–a)Do_2 gradients >600 mm Hg occurring over 12-hour periods were associated with 100 per cent mortality in infants with PPHN.[34] In 1986, Beck et al. reported that an (A–a)Do_2 gradient of >610 mm Hg for 8 hours was associated with a 79 per cent mortality.[3] In that series, 100 per cent mortality was reached by only an (A–a)Do_2 gradient of >630 mm Hg for at least 24 hours. In our study infants with PPHN generally did have increased (A–a)Do_2 gradients during the acute phase of their illness. However, many infants with reactive pulmonary vasculature decreased their gradients significantly in response to changing medical therapies (i.e., more aggressive hyperventilation, pressors, or vasodilators), thus, "resetting the clock." Therefore, an (A–a)Do_2 gradient of 600 to 630 mm Hg for

8 to 24 hours occurred late in the course of the illness and was not of clinical use in defining prognosis.

Use of this scoring system may facilitate further prospective, randomized studies on the use of ECMO, HFV, and less aggressive medical interventions in infants with PPHN. The scoring system presented here appears to aid in the selection of the highest risk infants by 24 hours of age. An accurate prognosis was established in 93 to 100 per cent of infants with PPHN. Infants who died were older (late gestational age), had evidence of perinatal asphyxia (lower pH and 5-minute Apgar score), and were more difficult to ventilate (higher IP, lower critical $PaCO_2$, higher ventilator rate) when compared to surviving infants.

SPECIFIC APPROACHES TO CLINICAL MANAGEMENT OF PPHN AND HOW THESE APPROACHES HAVE CHANGED OVER THE PAST 10 YEARS

Let us briefly review at this point some of the historical approaches to pulmonary hypertension. Currently, hyperventilation,[17,51] tolazoline,[29] dopamine,[21] volume expanders, and paralysis have been advocated as the central foci for clinical therapy in the pulmonary hypertension syndromes in infancy. Tolazoline or Priscoline therapy was suggested to be useful for pulmonary hypertension of the newborn in 1965.[14] Goetzman's article in 1977 was the first to describe a large series of infants treated in this way and indicated that tolazoline could result in increased Pa_{O_2}.[29] Subsequently, this therapy was widely used. Several reports, however, indicated that systemic hypotension was commonly observed with the use of this medication, and that there was a lower response rate in patients who were critically ill. Recommendations for tolazoline were summarized in a recent publication, which pointed out that tolazoline dose requirements for specific patients vary with renal dysfunction.[67] This article stressed that tolazoline doses derived from neonatal kinetics are less than current infusion recommendations and new dosage schedules may avoid high serum concentrations of the drug. They recommended that after the initial loading dose, an infusion of 0.16 mg of tolazoline per kg per hour for every 1 mg per kg loading dose should maintain a stable plasma concentration.

In 1977, preliminary data were presented indicating that hyperventilation producing a respiratory alkalosis had a consistent effect on decreasing pulmonary artery pressure in infants with PPHN.[52] In 1978, more extensive results were published indicating that a decrease in $PaCO_2$ was observed to decrease pulmonary artery pressure. This decrease in PCO_2, however, was produced by hyperventilation of the infant at relatively high ventilator pressures and rates, producing a simultaneous respiratory alkalosis. It was, therefore, difficult to determine whether CO_2 or pH was the primary factor involved in the improvement.[51] These observations were confirmed by Drummond

et al. in 1981, who also stressed the use of dopamine for raising systemic arterial blood pressure in these patients.[17]

Subsequently, a review paper described a clinical scheme employing the concept of "critical pCO_2" to aid in the clinical management of these infants by serially documenting and controlling pCO_2.[22] Many of these patients had metabolic acidosis associated with their primary condition, so that the effect of pH alone was more difficult to interpret for the clinical management of these patients. Other papers, however, have suggested pH is an important factor in control of pulmonary artery pressure in these infants.[59] Earlier physiologic literature in animals suggested that pH was a major factor in the control of pulmonary vascular resistance.[55] There were few papers describing the relationship of either alveolar or arterial PCO_2 concentrations and pulmonary vascular resistance. An article by Cassin et al. indicated that in fetal animals, Co_2 also had a role in controlling pulmonary vascular resistance.[12] Anecdotally, however, in our institution for a 1-year period prior to the institution of hyperventilation, we used intravenous sodium bicarbonate to produce marked metabolic alkalosis (pH up to 7.7) and normal PCO_2s with an unsatisfactory response in PAP in a group of infants with persistent pulmonary hypertension.

The publication of an article in 1985 entitled "Management of Infants with Severe Respiratory Failure Without Hyperventilation" has stirred up discussion relative to the merits and necessity of hyperventilation.[68] In this paper, 15 infants with high $(A-a)DO_2$ gradients were treated without hyperventilation. $PaCO_2$ was not controlled rigidly and was allowed to rise as high as 60 mm Hg. It is difficult to consider this group of infants as having severe persistent pulmonary hypertension since 6 out of the 15 had either respiratory distress syndrome or transient tachypnea of the newborn as a predisposing factor and 9 out of the 15 infants required 7 days or less of mechanical ventilation. This study needs further confirmation to see if the authors are describing an equivalent type of critically ill patient with persistent pulmonary hypertension, as has been reported in other series to determine if this mode of therapy has any long-term consequences. In addition, there are no followup data from the patients in this series, and other authors have reported satisfactory followup after hyperventilation.[16] It is clear to most clinicians that hyperventilation therapy should be reserved for the most severely ill infants with persistent pulmonary hypertension and should be instituted only after a diagnosis of pulmonary hypertension is established. From a clinical standpoint this includes (1) decreasing PaO_2s in spite of 100 per cent inspired oxygen concentration, (2) severe retractions, (3) requirement for mechanical ventilation, and (4) confirmation of right-to-left shunting with a two-dimensional or a contrast echocardiogram. In addition to these tests, Drummond uses auscultation of a loud second heart sound without splitting as a bedside test to serially evaluate pulmonary artery pressure.[16] As the pulmonary artery pressure decreases, the second sound decreases in intensity as splitting occurs,

indicating that pulmonary artery pressure levels have decreased and attempts to wean can be initiated.

There are several recommendations for current therapy during hyperventilation that vary from previously reported management schemes. In the acutely ill infant during the first 24 hours, or infants exhibiting sudden decreases in P_{O_2}, the arterial P_{O_2} concentration should be left at approximately 100 mm Hg.[22, 23] After the infant has exhibited stability, P_{O_2} levels of 60 to 70 mm Hg are usually adequate. Perhaps the biggest change in mechanical ventilator management at this time is the use of either slower or higher ventilator rates than were initially recommended. In the initial articles, ventilator rates as high as 100 to 150 breaths per minute were recommended in the acute stages of illness. Most infants are now being managed with 60 to 80 ventilator breaths per minute. Especially in meconium aspiration syndrome, rates of 60 breaths per minute appear to be more efficacious in managing these infants primarily because they have obstructive airway disease and need prolonged expiratory time to prevent air trapping. At ventilator rates above 80 to 90 breaths per minute, serial x-rays or lung pressure–volume curves should be determined to ascertain that air trapping is not a significant problem. The exception to this approach occurs when high-frequency jet ventilation (HFJV), a radically alternative mode of ventilation, is employed. This approach is described in the next section.

HIGH-FREQUENCY VENTILATION FOR THE TREATMENT OF PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Conventional mechanical ventilation has dramatically reduced mortality and morbidity in neonates with respiratory disease. However, infants continue to die of respiratory failure during the acute phases as well as chronic phases of their disease, and the incidence of bronchopulmonary dysplasia appears to be steadily increasing.[49] BPD, currently defined as oxygen dependency at 1 month of life, has been directly associated with treatment by positive-pressure ventilation and increased inspired oxygen concentrations.

The lung injury that results from aggressive treatment of full-term infants with PPHN can lead to a similar form of chronic lung disease.

Because it is thought generally that the primary factors responsible for the development of chronic lung disease are high inspired oxygen concentration and high peak inflating pressures, much work has focused on alternative techniques to provide adequate gas exchange in infants. One of the recent alternatives to the ventilation of the newborn is the use of HFV.

HISTORY OF DEVELOPMENT OF HFV

The first observation that gas exchange adequate to support life could occur with tidal volumes less than anatomic deadspace was

made by Henderson in 1915[31]; this phenomenon was observed in panting dogs. During the late 1950s, Emerson developed a rotating ball flow interrupter that was capable of respiratory rates as high as 2000 breaths per minute. This device was designed for physiotherapy of patients with chronic lung disease. It was noted, however, that during the application of this technique, gas exchange continued, and ventilation and oxygenation could be maintained. During the 1960s and 1970s, Sjostrand and associates in Sweden,[62] Lunkenheimer et al.,[38] and Bryan and associates in Canada,[10] as well as a number of investigators in the United States, began to apply low-volume HFV techniques in both experimental and clinical situations. Several reports[6, 7] during the 1970s used the technique of high-frequency low-pressure ventilation, usually at rates from 60 to 150 breaths per minute in the treatment of respiratory distress syndrome (RDS). In 1981, Marchak et al.[39] reported the first successful use of high-frequency oscillatory ventilation in the treatment of RDS. Since then, many investigators have performed studies in both humans and animals that have established the efficacy of HFV in a variety of clinical and experimental situations.

PHYSIOLOGY

Presently the mechanism by which HFV produces gas exchange is not completely understood. During spontaneous breathing, gas transport in the large airways occurs primarily by convection. This form of bulk transport exists until approximately the eighth to ninth airway division. As airways continue to narrow beyond this point, the cross-sectional area decreases dramatically, convective velocities decrease, and radial diffusion becomes an increasingly important transport mechanism. By the time gas reaches the alveolus, velocity of convection approaches zero and gas exchange occurs primarily through a combination of axial and molecular diffusion.

In contrast, techniques that have attempted to measure gas flow during HFV have been hampered by the difficulty in measuring airway pressures or flow in living animals at the frequencies under study. Furthermore, the variety of frequencies chosen by many investigators have raised the question of applicability of findings to all ranges of high frequency (1–50 Hz) that have been studied. It is likely, however, that mechanism gas exchange during high HFV is not dramatically different than that occurring during spontaneous or conventional ventilation.

One of the primary difficulties in describing the physiologic effects of HFV arises from the fact that with most forms of high frequency, the tidal volume is less than deadspace volume. If one assumes that alveolar ventilation equals the product of ventilatory frequency and tidal volume minus the deadspace volume, then it is apparent that, if deadspace ventilation exceeds tidal volume, alveolar ventilation must be zero! As a result, during HFV, gas dispersion must

be enhanced so that less convective flow occurs in the airways and diffusion of gases is somehow increased. Theories such as augmented diffusion[27] in large airways, and coaxial diffusion,[60] have been proposed as mechanisms through which HFV may exert its unique effects. Although these models are attractive, they have yet to be demonstrated physiologically. Augmented diffusion refers to a process by which the high frequencies used during therapy increase the rate of gas transport through the airways. Coaxial diffusion is thought to be a mechanism by which fresh gas travels rapidly down the center of the airway, while carbon dioxide elimination occurs along the periphery of the airway. An interesting corollary to the coaxial diffusion theory suggests that carbon dioxide movement occurs in a spiral fashion, thus producing a whirlpool effect that helps move the fresh inspired gas down the central portions of the airway.

The effects of HFV on pulmonary function have not been established or studied, nor have the effects of high frequency on the cardiovascular system and cardiovascular-pulmonary interaction[63] been clearly described. The surfactant system does not appear to be interrupted[26] during HFV and our experience with some infants suggests that high frequency may in fact enhance surfactant release. Further work in these areas should be forthcoming in the near future.

TYPES OF HIGH-FREQUENCY VENTILATION

At the present time, HFV can be divided into three basic classifications: (1) high-frequency positive-pressure ventilation utilizing currently available neonatal ventilators at rates of up to 150 breaths per minute; (2) HFJV and high-frequency flow interruption that provide a positive pressure flow to the patient that is interrupted at a preset frequency with passive exhalation of gases; and (3) high-frequency oscillatory ventilation that provides flow in and out of the airway at preset frequencies. In addition, several investigators have used combinations of conventional and HFV to achieve improved gas exchange in patients with a variety of neonatal lung diseases. These mixed mode therapies as well as standard HFV appear to be effective in a variety of clinical situations. Each of these forms of therapy will be discussed separately.

HIGH-FREQUENCY POSITIVE-PRESSURE VENTILATION

In general, high-frequency positive-pressure ventilation is a form of therapy that developed primarily during the late 1970s for the treatment of both respiratory distress syndrome[6, 7] and persistent pulmonary hypertension[5] of the newborn. For this form of therapy, no modification had to be made to conventional neonatal mechanical ventilators, with the exception of an increase in ventilatory frequen-

cies to rates of 150 breaths per minute. The goal in this form of therapy was to increase frequency, reduce tidal volume, and consequently reduce barotrauma to the lung. With these techniques, mean airway pressure did not change significantly, but peak inflating pressure was reduced. Although this procedure has proved helpful in the management of many infants, there are some inherent problems with conventional ventilators modified to produce these high ventilatory rates. Inapparent positive end-expiratory pressure, unrecognized air trapping, and decreased lung compliance may all result if the clinician is not aware of these potential undesirable effects. In addition, some concern has been raised that the tidal volumes delivered by this form of ventilation are not reduced sufficiently to prevent barotrauma. In fact, the shearing forces placed on the neonatal airway as these rates are generated may actually enhance airway injury. In general, therefore, units designed specifically for high frequency have increased in popularity to achieve the desired ventilatory therapy.

HIGH-FREQUENCY JET VENTILATION AND FLOW INTERRUPTION

In HFJV and high-frequency flow interrupters, a flow of gas is delivered to a patient from a pressurized source. Interruption in the flow is caused by a solenoid system or series of valves that produce pulsatile bursts of gases. In these forms of ventilation, expiration is passive. HFJV usually delivers pulsed gases through a cannula or specialized endotracheal tube within the airway, whereas high-frequency flow interrupters interrupt the gas flow at a position further from the patient. With these devices, tidal volume is generally near deadspace ventilation, although on occasion it may slightly exceed it.

At The Children's Hospital of Philadelphia, HFV has been available as a mode of therapy for the past 4 years. During this time, 148 patients have been treated with HFJV. Of these, 56 per cent (82 patients) have survived. In all cases, treatment was initiated as a "rescue" operation for lung disease when the ability of conventional ventilators to effect adequate gas exchange was inadequate, or conditions in which pulmonary air leak had become so significant that continued use of conventional mechanical ventilation was felt to be contraindicated. Although respiratory distress syndrome complicated by pulmonary air leak has been the most frequently treated disease, infants with meconium aspiration syndrome, persistent pulmonary hypertension of the newborn, group B streptococcal pneumonia, and pulmonary hypoplasia associated with congenital diaphragmatic hernia have also been treated successfully.

APPROACH TO TREATMENT WITH HIGH-FREQUENCY JET VENTILATION

In utilizing HFJV to treat the neonate with pulmonary disease, the clinician must be prepared to modify some of the approaches that

are used with conventional mechanical ventilation. In addition, the combination of HFJV with intermittent mandatory ventilation adds a previously nonexistent complexity to respiratory care. The approach to the use of HFJV at The Children's Hospital of Philadelphia will be outlined in some detail in the hope that this information will be of value to other clinicians who embark on this mode of therapy.

Presently, nearly all infants who ultimately are treated with HFJV have had their therapy initiated with conventional mechanical ventilation. In the future, HFV may be appropriate as an initial therapy. Pending data demonstrate that high frequency is superior to conventional ventilation. At this time, however, it seems appropriate to use HFJV only in cases where conventional mechanical ventilation appears to be failing or the neonatal lung disease is complicated by air leak in the form of pulmonary interstitial emphysema, pneumothorax, or pneumomediastinum.

To begin HFJV the patient needs to be reintubated with a special triple-lumen endotracheal tube (Hi-Lo Tube, Mallinckrodt Inc.). The three lumens consist of a main port through which PEEP is delivered by a conventional ventilator, a port for the jet pulse, and a pressure-sensing port at the distal tip of the endotracheal tube. Airway pressures on conventional ventilators can be measured with this tube in place. It should be noted that the external diameter of this tube is 0.3 to 0.5 mm larger than that of a conventional ET tube with a similar internal diameter. In general, our basic approach to the child who has air leak syndromes is to start HFV (Bunnell Life Pulse, Bunnell Inc., Salt Lake City, Utah) at a rate of 420 breaths per minute, a jet valve on time of 0.02 seconds, and a PIP of approximately 80 per cent of that being delivered by the conventional mechanical ventilator.

For the initiation of treatment in the patient with PPHN or meconium aspiration, we do not change the PIP at which we start HFV from that being delivered by the conventional mechanical ventilator. In general, this provides some hyperventilation that, by itself, may be beneficial in these diseases. We have found, however, in cases in which we have started HFJV at peak pressures lower than that, on the conventional mechanical ventilator, some infants with severe pulmonary hypertension may show acute deterioration. As a result, it appears preferable to start at the same PIP in PPHN and gradually decrease the peak pressure as determined by arterial blood gases in the infant. As with conventional ventilation, decreases in PIP or FiO_2 in the child with PPHN should be done very gradually to avoid sudden worsening of the infant's condition.

Transcutaneous monitoring, including $TcPO_2$, $TcPCO_2$, and pulse oximetry, is always used when initiating high frequency to be sure that the initial ventilator settings chosen are appropriate. If the transcutaneous changes appear reasonable, blood gases are drawn within 15 to 20 minutes following the initiation of HFV to assess the correlation between transcutaneous values and measured arterial blood gas values, and to further adjust ventilatory settings.

When pulmonary interstitial emphysema (PIE) or pneumothorax

is substantial, the initial therapy may consist of HFV only for a period of 6 to 24 hours. This is done to allow for the optimal resolution of air leak. It has been our experience that the continuation of HFV alone for periods longer than 24 hours usually results in atelectasis unless some type of sigh is provided for the infant. Furthermore, oxygenation can be substantially improved by the addition of background intermittent mandatory ventilation (IMV) in conjunction with the Bunnell Life Pulse Ventilator. Because the use of the Life Pulse requires a conventional ventilator to provide PEEP, with the two units connected in tandem to the patient, it is relatively simple to use a mixed-mode therapy of HFJV and IMV. IMV is usually instituted in conjunction with the Life Pulse at a rate of five breaths per minute, pressures approximately 2 to 5 cm of water below the peak inflating pressure of the jet ventilator pressures. Measurements of peak inflating pressure in animal studies done in our laboratory have indicated that during sighs, the peak pressures on the jet ventilator (as provided by the conventional mechanical ventilator) do not act in a directly additive fashion. When a sigh breath is given at a time when HFJV is operating, the peak pressure measured distally in the airway increases by only a few centimeters of water. This increase is not likely to produce significant additive barotrauma to the lungs.

In the initial stages of the use of HFJV, our experience has been that jet valve time and rate contribute very little when altered, as compared to manipulations of peak inflating pressure. For the infant, therefore, the elevated $PaCO_2$ is brought down into an acceptable range (between 20 and 50 mm Hg). If oxygenation is inadequate, three things can be done: (1) end-expiratory pressure may be increased; (2) the frequency of background ventilation with conventional ventilation may be increased; or (3) the frequency of background ventilation with conventional ventilation may be increased to a rate as high as 20 breaths per minute. These maneuvers improve oxygenation in babies treated with HFV. In the same manner, weaning is accomplished primarily by decreasing peak inflating pressure by 1 cm H_2O at a time when $PaCO_2$ is less than 40 mm Hg. The rate and jet valve time are usually not altered at all with jet ventilation. One should be cautious not to wean too rapidly because we have often seen that with HFV, excessively rapid weaning may lead to "flip–flop" and prolong the need for ventilation. In the same way, as oxygenation improves, inspired oxygen concentration and end-expiratory pressure may be lowered as determined by arterial blood gases. In addition, if background IMV is at 15 to 20 breaths per minute, this background ventilation also may be decreased.

At the present time, once the PIP is 20 cm of water or below, and there is an inspired oxygen concentration of 50 to 60 per cent or below, most infants are returned to conventional mechanical ventilation. We have weaned infants from HFV to CPAP on several occasions. The transfer back to conventional mechanical ventilation is currently a precautionary measure, until we learn more about the effects of long-term HFV.

A number of cautions should be added at this time. First, elimination of carbon dioxide through HFV is often enhanced more than improvement in oxygenation. As a result, one occasionally sees infants with a $PaCO_2$ in the 25 to 35 mm Hg range who achieve adequate oxygenation ($PaCO_2$ of 50–75 mm Hg) only at these low $PaCO_2$ levels. Attempts to reduce PIP in many of these infants may cause a serious deterioration of PaO_2. In some cases, however, PEEP may be increased with a simultaneous reduction in PIP to achieve a desired effect. Often this approach results in somewhat unusual pressure settings (i.e., PIP of 17 cm H_2O with a PEEP of 10 cm H_2O). In our followup studies to date we have not found any harmful effects from these relatively low $PaCO_2$ levels. The fact that they can be achieved with HFJV at PIP substantially below the PIP previously required with a conventional ventilator previously used on the same infant suggests that the lung is not overinflated but elimination of carbon dioxide is more efficient. One must be aware, however, that in some instances, especially at higher HFJV rates, air trapping can occur. We have rarely experienced this at rates below 500 breaths per minute with the Life Pulse ventilator.

Suctioning for infants on HFJV usually is carried out with the Life Pulse in the standby mode. We suction on standby to avoid shearing forces in the trachea produced by the combination of negative pressure suction and high-frequency positive-pressure breaths occurring simultaneously within the airway. With the "Hi/Lo" endotracheal tube used with the Bunnell Life Pulse, suctioning is done through a main port that attaches to the conventional ventilator while the high-frequency jet breaths are delivered through a separate port. It is our belief that the cessation of high frequency during suctioning, as well as the use of background IMV breaths may be one of the primary reasons why our unit has experienced no significant problems with necrotizing tracheobronchitis to date. This complication has been frequently reported at several other centers using HFV.[8]

Occasionally infants will require higher rates on the Life Pulse ventilator. To date, we have not treated infants who benefited from rates above 600 breaths per minute, although there are reports of infants treated at other centers with the Life Pulse who required rates as high as 900 breaths per minute. Again, manipulation of the rate on the Bunnell Life Pulse should be considered when other measures such as alteration of PIP do not seem to be contributing to improvement in the patient's ventilation.

Since we have found that rates of 420 and jet valve times of 0.02 second are optimal for the large number of infants that we ventilate, weaning from the ventilator is relatively straightforward. As the infant's condition improves (as demonstrated by lower $PaCO_2$ levels), weaning is accomplished by decreasing PIP by 1 cm H_2O at a time followed by a blood gas within 10 to 15 minutes.

Results of treatment of pulmonary hypertension with HFJV to date have been extremely encouraging. In a series of 30 babies with PPHN treated during the past 4 years at The Children's Hospital

of Philadelphia, 20 (67 per cent) have survived. All of these infants had failed conventional mechanical ventilation so that the expected mortality was approximately 100 per cent. Etiology of pulmonary hypertension in these infants included meconium aspiration syndrome, perinatal asphyxia, congenital diaphragmatic hernia, and Group B streptococcal infection. Fifty per cent of these infants, in addition, had suffered tension pneumothoraces on conventional ventilation prior to institution of HFJV, adding to the critical nature of their ventilatory support.

The general approach to therapy in these infants utilized the concepts of hyperventilation.[51] Since carbon dioxide elimination with resulting pH increase is typically enhanced by HFJV, infants could be ventilated at substantially reduced peak (PIP) and mean ($\overline{Paw}$) inflating pressures, while maintaining oxygenation of 80 to 100 mm Hg. For most infants, a 20 to 30 per cent reduction in PIP and $\overline{Paw}$ was noted. Total time of HFJV and IMV combined for survivors was 10.4 days. These results suggest that HFJV is a valuable alternative to conventional ventilation and is approximately as effective as ECMO with substantially less cost to the infant and medical care facility.

In our experience, few complications arise due to HFJV. As mentioned previously, we have not experienced significant necrotizing tracheobronchitis in any baby, even those treated for prolonged periods of time (>1 week). The reasons why our experiences differ from those at other centers remain unclear at present. As noted earlier, the approach to suctioning and the use of background ventilation may be important contributing factors in the reduction of this complication. Intraventricular hemorrhage (IVH) does not appear to be increased in infants treated with HFJV. Recent evaluation of infants treated to date shows that in infants weighing less than 1.2 kg, 27 per cent of babies had Grade III or IV IVH, whereas in babies more than 1.2 kg only 15 per cent had Grade III or IV IVH. Over 70 per cent of all infants had no detectable IVH seen on ultrasound examination. These results compare favorably to studies in infants on conventional ventilators. Followup studies done at 1 year of age are also encouraging. Most survivors of HFJV examined at 1 year of age appear to be neurologically and developmentally normal and have a normal respiratory status as well. It therefore appears that jet ventilation is a therapy with significant potential even in the most critically ill infants. Further controlled studies need to be undertaken to determine the safety of this technique as an initial therapy for the neonate with lung disease.

FOLLOWUP

Most infants diagnosed as having PPHN and treated with the therapies described in this article have little residual pulmonary symptomatology at 1 year of age. This group generally weaned rapidly to room air, began to feed well, and gained weight adequately. In addition, they have little evidence of neurologic or developmental com-

promise.[5] Some infants with more severe lung damage initially, especially those with the primary diagnosis of meconium aspiration, may have residual pulmonary symptomatology. Many of these infants will require fluid restriction, diuretics, or bronchodilator therapy even after discharge for mild respiratory compromise such as persistent tachypnea or tachycardia, mild right-sided failure, or evidence of bronchospasm. Some infants may even continue to require supplemental oxygen either continuously or intermittently during feedings or other periods of increased energy expenditure.

In those infants with persistent pulmonary symptomatology, close attention should be paid to maintaining adequate nutrition during the critical time shortly after discharge when the child is not being monitored by medical personnel on a daily basis. Oxygen consumption may be increased and metabolic demands are often greater than those of normal term or even preterm infants. These infants may be poor feeders, and weight gain is often slow. Adequate growth is crucial, however, since an increase in body mass is thought to be proportional to the growth of lung tissue and related to the "healing" of tissue damaged by the initial pulmonary insult during their neonatal course. If weight gain is proceeding at less than 15 to 20 gm per day, an attempt should be made to increase the caloric intake without significantly increasing fluid intake by either using more concentrated formulas or using formula additives.

Adequate weight gain is often a sign of stable or even improving lung disease. If these infants grow well and demonstrate clinical stability, attempts at slowly weaning them off of their supplemental oxygen can begin. If one has access to a noninvasive way of monitoring oxygen saturation, such as a pulse oximeter, its use can prove to be an invaluable tool in helping to decide how rapidly to wean. This approach usually is initiated within 1 month after discharge and may take up to several months to complete.

As the child gains weight, he or she will naturally begin to outgrow any medication that he or she had been receiving since the time of discharge. As long as he remains symptom free, this can be allowed to continue until the doses become subtherapeutic on a milligram per kilogram basis. In particular, it is rarely necessary to increase diuretic therapy to keep pace with weight gain unless the child continues to show signs of fluid overload. This same rule applies to bronchodilator therapy, unless the infant continues to demonstrate residual bronchospasm or other related respiratory symptomatology.

In children with residual lung disease, a simple cold or upper respiratory tract infection may progress rapidly to bronchiolitis or bronchopneumonia. These illnesses often are heralded by the development of bronchospasm. Bronchospasm often is triggered by viral infections, environmental irritants, or changes in fluid status. The airways are quite hyperreactive, and in many respects the clinical presentation is similar to that seen in children with asthma. Wheezing can be heard on auscultation and at times by the unaided ear. Unlike asthmatics, however, most infants with bronchospasm due to under-

lying residual lung disease outgrow the condition by 1 to 2 years of age. Because physicians are not accustomed to seeing a child present with bronchospasm before the age of 1 or 2 years, these infants are often diagnosed incorrectly as having bronchitis or pneumonia. Because of the possibility that a bacterial infection has triggered these symptoms, the infant is given antibiotics. Antibiotics, however, are rarely warranted unless a bacterial pneumonia is documented or strongly suspected. Cough medicine often is given because persistent coughing is a common presenting symptom in children with bronchospasm. Cough syrups, however, are ineffective because they do not treat the underlying bronchospasm and may delay the initiation of an effective therapy. Appropriate intervention for this type of bronchospasm includes the use of bronchodilators. Despite classic teaching, affected infants do have bronchial smooth muscle that is responsive to such medication. Most are discharged on theophylline or, less frequently, metaproterenol sulfate (Alupent, Metaprel). Theophylline is well tolerated in dosages similar to those used in asthmatics (4 to 6 mg per kg per dose every 6–8 hours). These infants need to be monitored closely for evidence of theophylline toxicity such as tachycardia, vomiting, and irritability. Metaproterenol may be used alone or in conjunction with theophylline and has the advantage of not requiring blood levels. The recommended dosage is 2 mg per kg per day in three or four divided doses.

Bronchodilators can be used during acute episodes either for short periods (3–7 days) or for several weeks until symptoms resolve. If improvement does not occur, medications may need to be adjusted or other possible causes of the bronchospasm may need to be investigated. As with asthmatics, maintenance on theophylline or metaproterenol may be necessary if the baby is experiencing recurrent episodes of bronchospasm. During acute exacerbations, a combination therapy (metaproterenol added to theophylline, for instance) can function synergistically to achieve the desired relief. This method has spared infants repeated trips to the hospital.[4]

In children whose primary diagnosis was asphyxia and who then developed PPHN, hearing and vision screenings should be performed. Infants with an Apgar score of less than 3 are at particular risk for permanent sensorineural hearing loss and should be formally evaluated by an audiologist using observation of behavioral responses or electrophysiologic reactions, the most common of which is brain stem evoked response audiometry. This can be done either just prior to initial hospital discharge or within the first 6 months of life. An ophthalmologic evaluation should be performed since these children are at risk for optic atrophy or cortical blindness.

Although there is some disagreement in the literature about the neurologic and developmental outcome of children with PFC, our experience has proved that, in general, these children have an excellent prognosis. It should be reemphasized that most infants with PFC who recover after treatment have complete resolution of their illness and have no neurologic or developmental compromise. Those

infants that we continue to follow because of residual lung disease are at the higher risk for significant sequelae. Most were severely hypoxic and required treatment with HFV (resulting in a relative hypocarbia) and pharmacologic intervention. Virtually all have normal neurologic and developmental outcome. Of those we have followed who do demonstrate some abnormality, residual muscle tone abnormalities are most common. When present, they are felt to be either transient dystonias or so mild as to not interfere significantly with the normal attainment of gross or fine motor milestones. The mean 6-month mental developmental index (MDI) using the Bayley Scales of Infant Development in our population is 105 ± 8, and PDI (Psychomotor Developmental Index) is 103 ± 11. At 12 months, their mean MDI and PDI are 104 ± 7 and 100 ± 10 respectively. Most children are progressing so well that we discharge them from close neurodevelopmental followup at 1 year of age. Only one child who was severely asphyxiated has developed a moderate to severe hearing loss and has been successfully fitted with hearing aids. She also is the only child we have evaluated who has developmental scores below normal for age.

SUMMARY

Despite these infants' very significant medical instabilities, which require vigorous therapeutic intervention, we have seen a population of infants with little in the way of persistent residual problems. Although many of their pulmonary complications persist after hospital discharge, most resolve within the first year of life. In addition, there are few neurodevelopmental disabilities encountered in such a high-risk population of children.

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