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Maternal Infection and Adverse Fetal and Neonatal Outcomes

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The relationship between pregnancy outcome and maternal colonization with a wide variety of bacterial, fungal, protozoan, and viral organisms has been studied for many years [1,2]. The more classic sexually transmitted diseases, including syphilis, gonorrhea, herpes, trichomonas and *Chlamydia*, are almost always transmitted between adults as a result of sexual contact. The majority of human immunodeficiency virus (HIV) infections in women of reproductive age are also transmitted sexually; however, there are other maternal infections that are not easily classifiable. Group B streptococcus, hepatitis B virus, cytomegalovirus, and the organisms associated with bacterial vaginosis, such as the mycoplasmas, *Gardnerella vaginalis*, *Bacteroides*, and *Mobiluncus* species, are all found more commonly in sexually active women than non–sexually active women, but their mode of transmission is often not apparent. Other maternal infections that are associated with adverse pregnancy outcomes, including malaria, parvovirus, rubella, and listeria, are not generally transmitted sexually.

In this article, the authors define a number of adverse pregnancy outcomes, and then explore the evidence that various types of maternal infections are responsible for these outcomes, which include stillbirth and neonatal death; congenital anomalies; short-term neonatal morbidity such as intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), and necrotizing entrocolitis (NEC); long-term morbidity, including cerebral palsy and mental

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retardation; and preterm birth and fetal growth restriction. Before we address specific adverse pregnancy outcomes, however, it should be noted that several sexually transmitted diseases, such as gonorrhea and chlamydia, have been associated with a failure to achieve pregnancy, predominantly through fallopian tube damage. Additionally, fallopian tube damage secondary to chlamydia and gonorrhea infection is the leading cause of ectopic pregnancy, which complicates close to 100,000 pregnancies in the United States each year [3].

Measurement of pregnancy outcome

The specific definitions of the most important adverse pregnancy outcomes collected through the vital statistics reports are as follows: in most states, abortion is defined as a pregnancy which terminates or is terminated before 20 weeks' gestational age, whereas a stillbirth is usually defined as a fetus born at 20 weeks' gestational age or more having no heartbeat or respiratory effort. A liveborn infant is generally defined as an infant born at any gestational age having a heartbeat or respiratory effort. Death of a liveborn infant can occur in the neonatal period (in the first 28 days of life) or in the post neonatal period (between 28 days and 1 year of age). An infant death is defined as the death of a liveborn baby that occurs before 1 year of age, both neonatal and post-neonatal deaths. Perinatal mortality is frequently defined as the sum of fetal and neonatal deaths, although other definitions are used. Preterm birth is defined as a birth occurring before 37 weeks of gestation, and a growth-restricted infant is defined as one born at less than the 10th percentile birth weight for a specific gestational age. There are many definitions of long-term morbidity, but those children who have structural anomalies, blindness, deafness, cerebral palsy, or mental retardation are frequently defined as handicapped.

Routes of transmission

Adverse pregnancy outcomes associated with maternal infections can occur because of direct infections of the fetus or neonate, or because of infections that cause early delivery without directly involving the fetus. For those organisms that attack the fetus directly, the transmission may occur within the uterus via transplacental or ascending infection, or in the intrapartum period secondary to fetal contact with infected genital secretions or maternal blood. Postpartum transmission occurs through breast-feeding or other types of maternal contact.

Diagnosing intrauterine infection

In general, organisms causing intrauterine infections enter the uterus through the placenta or ascend from the vagina into the uterus through the cervix.

Organisms can be found in the space between the decidua and the membranes, within the membranes, in the amniotic fluid, or within the placenta or fetus. Over time, evidence has accumulated in support of the causal role of intrauterine infection in various adverse pregnancy outcomes. As a result, growing attention has been focused on the optimal criteria for diagnosing intrauterine infection. Obviously, finding organisms in one of the above locations, before possible contamination from the vagina after membrane rupture, conclusively proves colonization (but not necessarily an adverse outcome associated with that colonization); however, many of the early studies, and in fact many studies reported recently, do not use a positive culture or even a positive polymerase chain reaction (PCR) for bacterial or viral DNA as the standard for diagnosing intrauterine infection. Instead, histologic chorioamnionitis or white cell infiltration into the chorion and amnion is often used as the criterion for diagnosing an intrauterine infection. Furthermore, in recent years there have been many investigations in which various markers of intrauterine infection—including elevations in various cytokines such as interleukin(IL)-6, IL-1β, and IL-8, increases in some of the matrix metalloproteinases, and the presence of white cells in the amniotic fluid—have been used as surrogate markers for an intrauterine infection [4–9]. Although finding bacteria in the amniotic fluid or in the membranes must be considered the most important indicator of any intrauterine bacterial infection, in women in preterm labor, the correlations between bacteria in the membranes, histologic chorioamnionitis, and elevated cytokines are all reasonably strong [5].

Types of intrauterine infection

As stated above, infections within the uterus may be located: (1) in the space between the decidua and the membranes, (2) within the membranes themselves, (3) in the amniotic fluid, or (4) within the placenta or fetus. Studies suggest that infection is most commonly found adjacent to or within the membranes. Importantly, of the women who have infection in the membranes, only half also have bacteria in the amniotic fluid [10]. A far smaller percentage also have a fetal infection. This pattern suggests that most intrauterine infections move from the membranes to the amniotic fluid and then to the fetus.

Recent studies demonstrate that there are a wide array of clinical presentations associated with intrauterine bacterial infections. Some women who have an intrauterine bacterial infection develop clinical signs of a systemic infection, including fever, uterine tenderness, and an elevated white cell response. These women are labeled as having clinical chorioamnionitis; however, it is now clear that many women can have an intrauterine infection without having these clinical symptoms. For example, several studies suggest that only 5% to 10% of the women who have histologic chorioamnionitis or women who have organisms in the membranes have clinical chorioamnionitis [11]. Therefore, many investigators studying this issue now believe that intrauterine infection rarely presents as clinical chorioamnionitis. Instead, uterine contractions or preterm labor, or pre-

term rupture of the membranes, appear to be far more common presentations of intrauterine infection. Furthermore, it is likely that many women who have an intrauterine infection will have no signs or symptoms at all.

Early pregnancy loss

The incidence of first trimester spontaneous abortion is highly dependent upon how one defines pregnancy. Using the standard obstetric definition, which includes a missed period and a positive urinary pregnancy test between 4 weeks and 6 weeks after the last menstrual period, approximately 15% to 20% of all pregnancies end in spontaneous miscarriage. The etiology of these miscarriages is generally secondary to maldevelopment of the ovum and associated chromosomal abnormalities. It is very rare to spontaneously abort a normally developing fetus during the first trimester. In fact, most of the pathologic material from spontaneous abortions fails to demonstrate any fetal tissue whatsoever. In some reports, maternal infections such as syphilis, rubella, and HIV have been associated with early spontaneous abortion; however, there is little evidence that these infections play an important role in first trimester spontaneous abortion [12].

Second trimester abortions (ie, those that occur between the 13th and 20th week of pregnancy) differ substantially from first trimester abortions in that a fetus is nearly always present. Spontaneous second trimester abortions occur in approximately 1% to 2% of all pregnancies. Although the etiology of these losses is often less clear than that of those occurring at other times, second trimester losses certainly include anomalous fetuses, some having chromosomal abnormalities, and those losses which occur secondary to uterine malformations, incompetent cervix and leiomyomata [12]. Most of the spontaneous second trimester losses, however, occur in the face of a normal uterus and a normally developed fetus. In these cases, there is either ''spontaneous'' labor or rupture of membranes leading to delivery, or a fetal death that ultimately leads to delivery. Obstetric complications such as twin pregnancy, placental abruption, the presence of maternal anticardiolipin antibodies, or the lupus anticoagulant and fetal growth retardation are also associated with spontaneous pregnancy losses between 12 to 20 weeks' gestation; however, the relative importance of these etiologies is not well quantified. Because the etiology of so many of the second trimester losses is not clear, and a majority of them are associated with spontaneous labor and ruptured membranes, there is ample room to hypothesize that intrauterine infection, which has been implicated in both of these pregnancy complications, may also be an important etiologic component of spontaneous second trimester losses. Indeed, chorioamnionitis has frequently been described, and there are numerous case reports of amniotic fluid infection that have occurred during this gestational age period. Additionally, isolation of microorganisms from pregnancy products has been reported to be more common in women who have spontaneous midtrimester pregnancy loss when compared with women who have induced

abortions [13,14]. Furthermore, several treatment trials have shown a reduction in second trimester abortions with antibiotics.

Stillbirth

A stillbirth is one of the most common adverse outcomes of pregnancy. In the United States, a stillbirth occurs in nearly 1% (or 7 per 1000) of all births, and in the year 2000, there were nearly 27,000 of these events [15,16]. The fetal death rates are approximately twice as high in African American women compared with white women. Stillbirth occurs far more frequently in developing countries than in developed countries, with rates as high as 100/1000 reported in some areas. Worldwide, nearly 4 million stillbirths occur in developing countries yearly [17]. In many countries, and especially the most developed ones, over the last several decades there has been a significant reduction in stillbirths. For example, from 1970 to 1998 the stillbirth rate in the United States fell from 14.0 to 6.7 per 1000 births [16]. Much of this decrease has occurred in term or near-term stillbirths, and is mostly due to improvements in medical care [18,19]. With these changes, stillbirths now account for about half of all perinatal mortality and more than a third of all mortality from 20 weeks' gestation to 1 year of age.

Because of the reduction in term stillbirths in the United States over the last several decades, most stillbirths now occur in the preterm gestational ages. In a US multicenter study [18], approximately half of the stillbirths occurred before 28 weeks gestational age, and another third of the stillbirths occurred between 28 weeks and 37 weeks. In this study, and in a number of others, the etiology of many of the stillbirths was not clear; however, many of the early gestational age fetuses died in conjunction with spontaneous preterm labor or rupture of the membranes. Placental histologic changes consistent with chorioamnionitis are found frequently in association with these early stillbirths, and these mothers are also more likely to develop postpartum endometritis. Therefore, there is substantial reason to believe that intrauterine infection may contribute to the etiology of many stillbirths, either as an initiator of preterm labor, as an initiator of ruptured membranes, or as an initiator of fetal death that ultimately results in the birth of a stillborn infant.

In developed countries, 10% to 25% of all stillbirths appear to be caused by a maternal/fetal infection, whereas in developing countries, which often have far higher stillbirth rates, the relative contribution of infection may be even greater [19–21]. The authors have recently reviewed the relationship between various types of maternal infections and stillbirth [22]. In that review, we found that this relationship was strongly influenced by gestational age. The earlier the stillbirth, the more likely it will be related to an infection. For example, in one study [23], 19% of fetal deaths at less than 28 weeks were associated with an infection, whereas only 2% of term stillbirths were infection-related.

For a number of reasons, the relationship between maternal infection and stillbirth is often not very clear [21]. First, it is often difficult to know exactly

why a specific fetus died. For example, an autopsy of the fetus and histologic study of the placenta may have findings suggestive of both infectious and hypoxic etiologies. Second, simply finding histologic evidence of infection or specific types of organisms in the placenta or on the fetus does not prove causation, nor does finding serologic evidence of infection prove causation. Neither does the presence of organisms in internal fetal tissues, although this finding clearly increases suspicion of an infectious etiology. Third, infection may cause a stillbirth that initially may not appear to be related to infection at all. The stillbirths associated with rubella-induced congenital anomalies, or with the nonimmune hydrops caused by parvovirus, were not originally seen as infection-related. Finally, organisms that now are quite clearly associated with stillbirth, such as parvovirus and *Ureaplasma urealyticum*, are hard to identify, and are often not sought in studies of infectious etiologies of stillbirths [10].

Conceptually, infection may result in fetal death through many different pathways [19–23]. First, a maternal infection may lead to a systemic illness whereby the mother is severely ill. Perhaps because of the high maternal fever, maternal respiratory distress, or other systemic reactions to the illness, the fetus may die, although the organisms are never transmitted to the placenta or fetus. The increased fetal mortality associated with influenza epidemics or maternal polio is likely due to this phenomenon [24,25]. Second, the placenta may be directly infected without spread of the organisms to the fetus. In these situations, reduced blood flow to the fetus may result in stillbirth. The stillbirths associated with maternal malaria infection are likely due to placental damage [26]. Third, the fetus may be directly infected through the placenta or membranes, with the infectious organisms damaging a vital fetal organ such as the lungs, liver, heart, or brain. Examples of this type of infection include the fetal pneumonia associated with *Eschericia coli* or group B streptococcal chorioamnionitis, or systemic infections with viruses such as coxsackie A or B [27–29].

If an infection occurs very early in gestation, the fetus may not die, but may develop a congenital anomaly, with a fetal death occurring later secondary to the anomaly. Rubella infection has been associated with stillbirths via this mechanism [30,31]. And lastly, an infection in the uterus or anywhere else in the mother's body may precipitate preterm labor. Some of these fetuses, often deemed to be too small to be salvageable by cesarean section, cannot tolerate labor and are born dead. *U urealyticum* is an organism that may precipitate early preterm labor by infecting the fetal membranes without causing a fetal infection. A urinary tract infection with *E coli* is an example of a non–genital tract infection that might precipitate early preterm labor. Periodontal infections are also associated with preterm labor, but the mechanism by which periodontal disease is associated with preterm birth has not yet been elucidated [32].

Ascending bacterial infection, both before and after membrane rupture, with organisms such as *E coli*, group B streptococci, and *U urealyticum* is usually the most common infectious cause of stillbirth; however, in areas where syphilis is very prevalent, up to half of all stillbirths may be caused by this infection alone. Malaria may be an important cause of stillbirth in women infected for the first

time in pregnancy. The two most important viral causes of stillbirth are parvovirus and coxsackie virus, although a number of other viral infections appear to be causal. *Toxoplasma gondii*, leptospirosis, *Listeria monocytogenes*, and the organisms that cause leptospirosis, Q fever, and Lyme disease have all been implicated as etiologic for stillbirth. Table 1, from our review, updated to reflect a few new reports, describes each of the organisms that to date have been studied in relationship to stillbirth [22].

Neonatal death

Neonatal deaths are defined as those that occur within the first 28 days of life. In most Western countries, these deaths occur at a rate of between 3 and 7 per 1000 live births. In general, about 70% of these deaths are associated with a preterm birth, and 25% are associated with a major congenital anomaly, with the remainder due to asphyxia, sepsis, meconium aspiration, birth trauma, and more rare conditions such as immune or nonimmune hydrops. Infection as a specific cause of neonatal death occurs predominantly in preterm infants, and is often part of the picture that includes RDS, IVH, and NEC. Because of the multiple system failures, it is often difficult to define a single cause of death in these cases, but infection frequently plays a role.

In developed countries, group B-streptococcus is one of the most common organisms implicated in systemic neonatal infection, but many other organisms, mostly gram-negative, including those that normally colonize the vagina (*E coli, Klebsiella*) and those that are acquired in the nursery (often staphylococcus), have also been implicated in sepsis related neonatal deaths [33,34]. In many developing countries, neonatal group B streptococcal infections are rare and the contribution of gram-negative organisms to neonatal sepsis is proportionately greater. Many of these neonatal infections appear to be contracted in utero before delivery. For the most part, these organisms enter the fetus by way of the amniotic fluid, infecting the lungs, causing a fetal or neonatal pneumonia. Both group B streptococous and the gram-negative organisms cause meningitis as well. Finally, infections such as syphilis and some virus infections such as cytomegalovirus (CMV), varicella, echovirus, coxsackievirus, measles, and herpes simplex are clearly causal for neonatal death, as are other transplacentally transmitted infections such as listerosis and even occasionally tuberculosis. In any case, based on these reports, the authors estimate that in the United States and other developed countries, less than 10% of neonatal mortality is due to neonatal sepsis, pneumonia, and meningitis, with a much smaller portion of the mortality attributable to other infections. In lesser developed countries, the neonatal mortality rates are considerably higher and the contribution of infection considerably greater. For example, in Pakistan it is estimated that half of the neonatal mortality, or as many as 30 per 1000 live births, is infection related [35]. Overall, the World Health Organization (WHO) estimates that of the nearly 5,000,000 neonatal

Table 1
Maternal infections and stillbirths

Organism	Maternal disease	Comment
Spirochetes		
T pallidum	Syphilis	Major cause of SB when maternal prevalence is high
B burgdorferi	Lyme disease	Confirmed, but not a common cause of SB
B recurrentis	Tick-borne Relapsing fever	Of unknown importance as a cause of SB
Leptospira interrogans	Leptospirosis	Confirmed, but not a common cause of SB
Protozoa		
T brucei	Trypanosomiasis	Not a certain cause of SB
T cruzi	Chagas disease	Confirmed as a cause of SB in South America but of unknown importance
P falciparum *P vivax*	Malaria	Likely an important cause of SB in newly endemic areas or in newly infected women
T gondii	Toxoplasmosis	Confirmed, but not a common cause of SB
C burnetti	Q fever	Confirmed as a cause of SB but of unknown importance
Viruses		
Parvovirus (B-19)	Erythema infectiosum	Confirmed as a cause of SB and likely the most common viral etiologic agent
Coxsackie A & B	Various presentations	Confirmed as causes of SB and may be an important contributor
Echovirus	Various presentations	Confirmed as a cause of SB but of unknown importance
Enterovirus	Various presentations	Confirmed as a cause of SB but of unknown importance
Polio virus	Polio	Historically a cause of SB but since routine vaccination no longer seen in developed countries
Varicella-zoster	Chickenpox	Confirmed, but not a common cause of SB
Rubella	German measles	Confirmed, but no longer a cause of SB in developed countries
Mumps	Parotitis	Possibly historically, but no longer a cause of SB in developed countries
Rubeola	Measles	Possibly a cause of SB historically
Cytomegalovirus	Generally asymptomatic in adults	Rarely if ever a cause of SB
SARS virus	Respiratory illness	Case reports
Variola	smallpox	Historically a cause of SB but no longer seen
Lymphocytic choriomeningitis virus	Lymphocytic choriomeningitis	Not confirmed as a cause of SB and of unknown importance
HIV	AIDS	Associated with SB, but not likely causative

(continued on next page)

Table 1 (*continued*)

Organism	Maternal disease	Comment
Bacteria		
Escherichia coli	Generally asymptomatic	Confirmed and probably the most common organism associated with SB
Group B streptococcus	Generally asymptomatic	Confirmed as a common cause of SB
Klebsiella	Generally asymptomatic	Confirmed as a common cause of SB
Enterococcus	Generally asymptomatic	Confirmed
Ureaplasma urealyticum	Generally asymptomatic	Confirmed
Mycoplasma hominus	Generally asymptomatic	Confirmed
Bacteroidaceae	Generally asymptomatic	Confirmed
Listeria monocytogenes	Listerosis	Confirmed, generally transmitted transplacentally
Other bacteria including brucellosis, clostridia, agrobacterium radiobacter, salmonella, pseudomonas, etc.		Suggested by case reports
Chlamydia trachomatis	Pelvic infection	Suggested by case reports
Neiserria gonorrhoeae	Pelvic infection	Suggested by case reports
Mycobacterium tuberculosis	Tuberculosis	Confirmed by case reports, but rare in developed countries
Fungi		
Candida albicans	Thrush, vaginitis	Confirmed as a cause of SB by case reports

Data from Goldenberg RL, Thompson C. The infectious origins of stillbirth. Am J Obstet Gynecol 2003;189:863.

deaths that occur each year worldwide, up to 40%, or 2,000,000 deaths per year, are due to infection [36]. Of these, 800,000 deaths, mostly in developing countries, occur due to acute respiratory infections.

Post-neonatal deaths

In developed countries, post-neonatal deaths occur in approximately three infants per 1000 live births. Sudden infant death syndrome is the most common etiology, and congenital anomalies, accidents, and infection account for most of the other deaths. The most common infectious-related causes of post-neonatal mortality include meningitis, pneumonia, and diarrhea. Although deaths from these causes are rare in middle class women in western countries, they are more frequently seen in rural areas and among the poor. In underdeveloped countries, infection may cause up to several hundred infant deaths per thousand live births. Nearly all the infectious causes of neonatal mortality cause postneonatal deaths as well.

Long-term disability

In addition to mortality, there has been a wide range of permanent structural and neurological morbidity associated with maternally transmitted infectious diseases. These include: (1) structural congenital anomalies with a defect in one or more organs; (2) structural or functional damage to the brain resulting in decreased cognitive ability, mental retardation, or both; and (3) a motor disorder such as a diminution of fine or gross motor skills, or an increase in spasticity or athetosis such as that associated with cerebral palsy. These morbidities, in addition to blindness, deafness, and hydrocephalus, have all been associated with infectious diseases [1].

Cerebral palsy

Cerebral palsy is found in about 2 infants per 1000, but is far more common in preterm infants. For example, among the lowest gestational age infants who survive (23 and 24 weeks), between 25% and 50% end up having cerebral palsy. Perhaps the most commonly used definition of cerebral palsy is that of Nelson and Ellenberg [37], who defined cerebral palsy as "a chronic disability characterized by aberrant control of movement or posture appearing early in life and not the result of recognized progressive disease." Cerebral palsy is associated with damage to the upper motor neurons within the brain, and most cases present as excessive muscular tonus, spasticity with increased stretch reflexes, and hyperactive tendon reflexes. The authors also emphasize that cerebral palsy is a neuromuscular condition only, and does not imply alterations in cognitive function. Although children who have cerebral palsy are statistically more likely to have low intelligence quotients (IQs), mental retardation, or various types of seizure disorders, many children who have cerebral palsy have normal intelligence and are free of other types of neurologic disability [38].

Many bacterial and viral infections of the fetus, infant, and young child have been associated with cerebral palsy, although quantification is difficult [39]. For example, Stanley [40] notes that a fairly large number of cases of cerebral palsy associated with congenital rubella syndrome were described before the initiation of the rubella vaccination program, but this relationship rarely occurs in the United States today. Congenital infection with *Toxoplasma gondii* and CMV can also cause cerebral palsy. Older literature suggests that infection of the infant with measles, mumps, varicella, and rubella was once reported as a common cause of central nervous system (CNS) injury leading to cerebral palsy. Since the development of vaccines for many of the common childhood diseases, however, it appears that a viral etiology for postpartum acquired cerebral palsy is rare. Nelson [41] agrees, stating that although numeric documentation is lacking, judging from medical writing in the 19th century when infectious diseases were more frequent and less effectively treated, infection-related cerebral palsy was more common than it is now in developed countries. Because of these reductions, it appears that CMV

has become the most common viral infection associated with a cerebral palsy-like syndrome [39]. In addition to the infections described, herpes virus infection as well as meningococcal, pneumococcal, and group B streptococcal infections of the neonate also may manifest later in life as a cerebral palsy-like syndrome.

More important numerically, many studies now link chorioamnionitis to the development of cerebral palsy [42–44]. Nelson and Ellenberg [37], using data from the Collaborative Perinatal Project, showed that in low–birth weight infants, chorioamnionitis was associated with a tripling of the risk of cerebral palsy from 12 per 1000 to 39 per 1000 live births. Among term infants in that study, chorioamnionitis increased the risk of cerebral palsy from 3 per 1000 to 8 per 1000 live births. In a more recent study, Grether and colleagues [45] examined prenatal and perinatal factors related to cerebral palsy in very low–birth weight (VLBW) California infants. In this study, chorioamnionitis was associated with a fourfold increased risk of cerebral palsy. Even more recently, term infants who have evidence of chorioamnionitis had a significantly greater risk of cerebral palsy [46]. Murphy and coworkers [47], investigating the relationship of various antenatal and intrapartum risk factors to cerebral palsy in infants born at less than 32 weeks' gestational age, showed that in such infants, chorioamnionitis increased the risk of cerebral palsy from 3% in controls to 17% in infected infants.

In a number of other studies, intrauterine infection has preceded neonatal IVH, a precursor of cerebral palsy. For example, Groome and colleagues [48], using data from the March of Dimes multicenter study, showed that clinical chorioamnionitis was associated with a twofold to threefold increased risk of IVH. Damman and Leviton [49,50] have also explored the relationship between maternal intrauterine infection and evidence of brain damage in the preterm newborn. They revealed an association between intrauterine infection in the mother and both IVH and white matter damage in the newborn. In a study of more than 1000 preterm infants, intrauterine infection was associated with a doubling of the infant's risk for having IVH, periventricular leukomalacia (PVL), and ventriculomegaly. Additional data from the National Institute of Child Health and Human Development Neonatal Research Network [51,52] confirm that both early-onset and late-onset sepsis in VLBW newborns is associated with an increased incidence of IVH.

Bejar and coworkers [53] found that chorioamnionitis was present in more than half of the preterm infants who developed white matter echolucencies within 3 days after birth. Leviton [54] notes that the histologic abnormalities of white matter have been associated with sepsis in the baby and with gynecologic and urinary tract infection in the mother. Mays and colleagues [55] report that acute maternal appendicitis is associated with IVH and PVL, even when the gestational age at birth is controlled for. Therefore, even extrauterine intra-abdominal infections appear to be able to initiate the cascade of events linking infection, labor, and neonatal brain injury [56]. Hansen and coworkers [57] studied the correlation between placental pathology and IVH in preterm infants. Placental characteristics of inflammation, including umbilical vasculitis, chorionic vasculitis, and inflammation of the subchorion, chorion, and amnion, were associated with an

increased risk of IVH. Grafe [58], Salafia and colleagues [59], and others confirmed the relationship between both periventricular hemorrhage and leukomalacia and cerebral palsy and placental membrane and umbilical cord evidence of inflammation and associated thrombosis [60,61].

In a further attempt to understand this phenomenon, Kuban and Leviton [62] studied echolucent images in periventricular white matter in relationship to maternal uterine infection. The odds ratio for development of an echolucency was highest for infants whose placentas had vasculitis of the chorionic plate or umbilical cord (odds ratio = 9.8). Zupan and coworkers [63], in a study of risk factors for PVL, found a strong link between intrauterine infection and the development of PVL, and that this relationship was increased in the face of premature rupture of membranes and infection. They also suggest that most of the PVL originates before birth, that susceptibility to the condition closely depends on the developmental age, and that the major etiologic components of white matter lesions in infants born late in the second trimester relate to the presence of an intrauterine infection. Perlman and colleagues [64] noted that cystic PVL, which occurred in 3% of infants weighing less than 1500 g, was associated with two clinical indicators: prolonged rupture of membranes and chorioamnionitis. The odds ratio for cerebral palsy after prolonged rupture of membranes was 6.6, and the odds ratio for cerebral palsy with chorioamnionitis was 6.8.

In recent years, much evidence has emerged suggesting that various cytokines mediate the relationship between cerebral palsy and intrauterine infection, IVH, and PVL. Certainly various cytokines, such as IL-6, IL-1, tumor necrosis factor (TNF) alpha, and others, are elevated in the amniotic fluid of pregnant women who have chorioamnionitis. Andrews and coworkers [13] have emphasized that amniotic fluid cytokines are elevated even with infection confined to the amniotic membranes. Adinolfi [65] was among the first to propose that cytokines produced in relationship to maternal infection were harmful to the developing brain of the unborn infants. Figueroa and colleagues [66] showed that elevated amniotic fluid IL-6 predicted neonatal PVL and IVH. Yoon and coworkers [67], Kashlan and colleagues [68], and others showed that elevated IL-6 levels in the umbilical cord were also related to the subsequent development of periventricular echodensities and echolucencies. Recent papers document the association between elevated umbilical cord blood cytokine levels and cerebral palsy [69,70]. From these data, there seems little question that intrauterine infection, a clear predictor of preterm delivery [14], is also a predictor of white matter lesions, IVH, and ultimately cerebral palsy. If, as has been proposed [71], 70% to 80% of VLBW births are associated with an intrauterine infection, the high rate of cerebral palsy in these infants may well be related to this intrauterine infection.

Mental retardation

Mental retardation, usually defined by an IQ cutoff less than 70 or 75, is another outcome measure of great importance, but one whose prevalence in the

population is difficult to determine with certainty. Prevalence is undoubtedly influenced by definition, timing of testing, and many other factors as well, but in most populations about 3% of all infants and children receive this diagnosis. Babies born prematurely and babies born following intrauterine growth retardation are all at greater risk for the development of mental retardation regardless of the definition [72,73]; however, most babies who have these diagnoses will eventually have IQs within the normal range. For example, on average, infants who survive weighing less than 1000 g at birth, have an average IQ about 10 points below appropriate controls. As with cerebral palsy, intrauterine infection is thought to play a role in this reduction in IQ. What is clear, however, is that the socioeconomic status and educational background of the parents greatly influence the ultimate rate of mental retardation in the population. Although perinatal infections that attack the fetus, such as group B streptococcus, herpes simplex virus, CMV, syphilis, and toxoplasmosis all are demonstrated causes of mental retardation, infection-initiated preterm birth, which will be described in detail, appears to be a more important cause of mental retardation from the overall public health perspective [74,75].

Psychiatric disease/schizophrenia

A variety of psychiatric and developmental disorders, and especially schizophrenia, have been associated with various maternal infections. Prenatal influenza has been the most studied [76–78]. Interestingly, several recent studies have shown that increased levels of amniotic fluid cytokines during the second trimester of pregnancy may contribute to a greater risk in offspring developing schizophrenia [79]. Those relationships that are positive are at best associations, with no proven causality. Relationships between pre- and perinatal infections with childhood autism have also been studied, and as with schizophrenia, the data supporting the relationship are mixed. Further research is necessary to confirm or refute each of these relationships.

Congenital anomalies

Structural anomalies of the fetus occur in about 3% of all births. Among the most serious, and those that contribute to the most long-term morbidity and mortality, are neural tube defects, urinary tract anomalies, and cardiac defects. Overall, about 20% of stillbirths and neonatal deaths are caused by an anomaly, as is a portion of mental retardation. Although maternal virus infections clearly can cause structural anomalies, only a very small percentage of all anomalies are likely to be viral related. For example, rubella infections, especially those occurring in the first trimester, as well as varicella infections, are associated with a wide variety of anomalies. Because of routine vaccinations to prevent rubella and other viral infections, however, these anomalies are rarely seen today in de-

veloped countries. Coxsackieviruses B3 and B4 have been associated with congenital heart disease [80]. Maternal parvovirus infection, especially in the second trimester, has been associated with a fetal nonimmune hydrops, sometimes leading to fetal death. Whether it is appropriate to consider these cases as congenital anomalies is not clear. In addition, there are isolated case reports of CNS anomalies associated with parvovirus infection, but this relationship has not been confirmed epidemiologically.

Growth retardation

Fetal growth retardation is generally defined as a birthweight less than the 10th percentile birthweight for gestational age; however, the standards used to define the 10th percentile birthweight for gestational age are highly variable and often do not apply to the population being evaluated [81]. Also, because the gestational age measures used for defining the standard are so variable, it is difficult to compare rates of growth retardation from one time period to another, or from one study to another. Growth retardation has many etiologies, including low maternal height, low maternal weight, smoking, preeclampsia, congenital anomalies, and intrauterine infection. With changes in obstetric recommendations about maternal weight gain over the last several decades, it appears that the rate of growth retardation is decreasing.

Nearly all infections of the mother and fetus have been associated with growth retardation, but it is unknown whether maternally transmitted infections other than those that infect the fetus or placenta early and directly, such as rubella, toxoplasmosis, CMV, syphilis, and malaria, actually cause growth retardation. Assuming they do, the mechanism may lie in fetal cell death caused by direct infection or by changes in placental or fetal blood flow. Maternal malaria, for example, which often attacks the placenta and seems to inhibit gas and nutrient exchange, is associated with a two- or threefold increase in fetal growth restriction [26]. The impact of syphilis is similar, and in general, in developing countries, a wide variety of maternal infections are very likely responsible for a large proportion of the growth retarded infants. Because growth retardation in developed countries often appears to be associated with below average maternal size, poor nutritional status, various adverse health behaviors and hypertension, however, it is unclear what portion of the growth retardation in developed countries can be explained by an infectious etiology.

Preterm birth

Preterm birth is the most significant problem confronting obstetricians in industrial countries today. Preterm births, defined as those occurring at less than 37 weeks' gestational age, are associated with approximately 75% of the perinatal mortality and as much as 50% of the long-term neurologic handicap [82]. In the

last 20 years, the preterm rate in the United States has risen from approximately 9.5% to 12% [83]. Although we have made tremendous strides in keeping preterm infants alive, we have been less successful in reducing the long-term handicap rates among the survivors [84,85]. Much of the mortality and the long-term handicap associated with prematurity occurs in the smallest or earliest gestational age newborns. For example, it is estimated that 60% of the neonatal mortality and much of the long-term handicap accrue to infants born weighing less than 1000 g and less than 28 weeks' gestational age. Many of these early preterm births occur secondary to an intrauterine infection [86]. This section explores the relationship between infection and preterm birth.

The relationship between genital tract infection and preterm birth has been appreciated by some physicians for more than half a century. For example, in 1950 Knox and Hoerner [87] noted that "infection in the female reproductive tract can cause premature rupture of the membranes and induce premature labor." In their series, they noted that the membranes in all premature cases showed evidence of infection. Perhaps the most influential paper on infection and preterm birth was written in 1977 by Bobitt and Ledger [88]. In this study, they performed amniocenteses in 10 women in preterm labor with intact membranes. Seven of the women had bacterial colony counts higher than 1000 per mL, with anaerobic organisms predominating. These authors posited that bacteria can penetrate the fetal membranes and contaminate the amniotic fluid, and suggested that in patients in premature labor, the role of unrecognized amnionitis should be re-evaluated. Elder and colleagues [89] approached the issue of infection and preterm birth somewhat differently. Believing that bacterial infection was causal for preterm birth, in 1971 they treated 279 "non-bacteriuric women" with a 6-week course of 1 g of tetracycline daily beginning at less than 32 weeks' gestational age, and compared the outcomes to women treated with a placebo. In the tetracycline-treated group there were statistically fewer preterm births.

Because of the more frequent use of amniocentesis, we now have ample data relating amniotic fluid infection to preterm labor. Beginning with Bobitt and Ledger's study [88] and extending to the present, there have now been a large number of studies in which women presenting with preterm labor and intact membranes have had an amniocentesis performed and the amniotic fluid cultured [90–94]. The percent of positive cultures in these studies has varied widely, ranging from no positive cultures in several small studies to as high as 50% in others. In a review of the studies performed before 1992, 100 of 863 or 12% of amniotic fluid cultures were positive. Knowing what we know now, the reason for the relatively low culture rates are quite apparent. First, many of these studies did not focus on early preterm infants, and we know that the percent of positive cultures are gestational age-related, with the proportion of positive cultures increasing with decreasing gestational age [86]. Second, few of these studies cultured for *Ureaplasma* or *Mycoplasma* or other hard-to-grow anaerobes. We now know that the most common organisms found in the uterus are *Ureaplasma* and *Mycoplasma*. We also know that in the presence of an intrauterine infection, the amniotic fluid will be positive on only half the occasions when organisms are

present in the membranes [10]. For each of these reasons and possibly others, the rates of positive amnionic fluid cultures in women in preterm labor are lower than the actual rate of intrauterine infection.

Relationship to gestational age

A concept developed more than 20 years ago, but more widely held today, is that the relationship of intrauterine infection and preterm labor is not consistent across all preterm gestational ages. In 1979, Russell [95], using histologic chorioamnionitis as a marker of infection, showed that virtually all births at 21 to 24 weeks were associated with an intrauterine infection, compared with only about 10% of the preterm births at 33 to 36 weeks. Mueller-Heubach and colleagues [96] and Chellam and Rushton [97] reported similar findings, which were also confirmed by Andrews and coworkers [5] in Alabama. Therefore, there is no question that the earliest preterm births are strongly associated with histologic chorioamnionitis.

Rather than evaluating histologic chorioamnionitis as the marker of intrauterine infection, in 1992, Watts and coworkers [98] studied amniotic fluid cultures in women in labor who had intact membranes. They showed that at 23 and 24 weeks' gestation, more than 60% of the women in preterm labor had organisms in the amniotic fluid. That number fell to less than 20% for women in labor at 33 to 34 weeks. To further investigate this issue, Hauth and colleagues in Alabama [99] cultured the chorioamnions of over 600 women having a cesarean section who had intact membranes. In this study, after delivery the placental membranes were opened and cultures were taken from the space between the chorion and amnion. This study design precluded vaginal or ascending infection following membrane rupture contamination of the membranes, because membranes were not delivered through the vagina and the membranes were intact at the time of delivery. The study authors found that in women in spontaneous labor delivering a less than 1000-g infant, 83% had chorioamnion cultures that were positive, whereas those delivering a more than 2500-g infant had a 20% positive culture rate [99]. For those women not in labor, undergoing an indicated cesarean section, and delivering a less than 1000-g infant, only about 10% of the cultures were positive. The researchers therefore believe that based on histology and culture results, 80% or more of women in early preterm labor, destined to deliver a less than 1000-g infant, will have organisms in the membranes before membrane rupture. They believe this association is likely to be causal for preterm birth.

Chronicity

There is also ample evidence suggesting that intrauterine infections are often chronic. As evidence, intrauterine infections have been documented weeks or even months before a preterm birth [100–102]. For example, in Alabama, at the

time of routine genetic amniocentesis at 16 to 18 weeks, it was occasionally noted that the amniotic fluid was cloudy [100–102]. For this reason, fluids were sent for routine bacterial culture, and cultures for *Ureaplasma* and *Mycoplasma* were often performed. Occasionally the cultures were positive. In nearly all cases in which the amniotic fluid was found to be infected with *Ureaplasma*, the women were initially asymptomatic; however, many of these women went on to deliver spontaneously at 24 to 28 weeks' gestation without clinical chorioamnionitis. The placentas, however, were nearly always positive for histologic chorioamnionitis. Similarly, using PCR techniques for the diagnosis of *Ureaplasma* infection in amniotic fluid, it has been demonstrated that women who are PCR-positive are substantially more likely to experience spontaneous preterm labor later in the second trimester [103]. More recently, using IL-6 as a marker of infection, it has been observed in several series that women undergoing routine genetic amniocentesis at 16 to 18 weeks and who are found to have high amniotic fluid IL-6 levels frequently deliver at less than 32 weeks [104–106].

Organisms

Between 50 and 100 different organisms have been associated with intrauterine infections before the rupture of membranes [93,94]. What is interesting about these infections is that certain common vaginal organisms, such as group B streptococcus and *E coli*, are rarely found in the uterus before rupture of membranes. Furthermore, gonorrhea or *Chlamydia* are hardly ever found inside the uterus before membrane rupture. On the other hand, a number of other organisms, such as *Ureaplasma*, *Mycoplasma, Gardenerella*, *Mobiluncus*, *Peptostreptococcus*, and *Bacteroides*, are quite commonly found in the uterus before membrane rupture. Why some organisms invade the uterus before membrane rupture and others do not is not clear. Galask and colleagues [107] showed that neither *Chlamydia* nor gonorrhea bind to the fetal membranes, and offered the failure to attach as an explanation for their lack of entrance into the uterus before membrane rupture. What is clear about the organisms generally found in the uterus before delivery is that they generally are of low virulence. It may be that this low virulence accounts for both the chronicity described above and the fact that most of the intrauterine infections do not cause a clinical chorioamnionitis.

Mechanisms

The mechanisms by which an intrauterine bacterial infection precipitates preterm labor are relatively clear. Placing either living organisms or bacterial endotoxin into an animal's uterus under experimental conditions precipitates preterm labor in a fashion similar to that which occurs in humans with naturally acquired organisms [108]. In both cases, the intrauterine infection elicits an immune response that includes an increasing production of a wide variety of

cytokines, prostaglandins, and metalloproteinases [4,5,86]. These analytes are capable of causing contractions, cervical softening, and membrane rupture, which together ultimately result in spontaneous preterm birth.

Origin of the organisms

Conceptually, there are at least several pathways by which bacteria can enter the uterus. For example, if the mother has a bacteremia or viremia, organisms can enter the uterus hematogenously through the placenta. Although it is believed that hematogenous spread through the placenta is rare, it almost certainly does occur. As evidence, fetuses have been infected by a wide variety of organisms during maternal septicemia, including those causing *Listeria* and tularemia. These organisms appear to reach the fetus through the maternal circulation [22]. Dental organisms such as *Capnocytophaga* and various fusiform organisms are also most likely to enter the uterus through the placenta [109,110]. Theoretically, bacteria can enter the uterus through the fallopian tubes; however, the abdominal cavity is usually sterile. Organisms have been introduced inadvertently into the amniotic cavity at the time of amniocentesis, but this route of infection seems quite rare. Finally, and most commonly, it appears that bacteria from the vagina can ascend into the uterus through the cervix. The organisms most commonly found in the uterus are those typically found in the vagina, of which *Ureaplasma* is the most common. It is therefore widely believed that the organisms responsible for most early preterm birth are vaginal organisms that ascend directly from the vagina through the cervix into the uterus.

Timing of ascent

It is widely held that organisms from the vagina ascend into the uterus during the pregnancy, traversing the space between the membranes and the decidua. The bacteria then take up residence in the membranes, and in about 50% of the cases enter the amniotic fluid. In a much smaller percentage of the cases, the fetus is infected as well. An alternate hypothesis is that the organisms that ultimately cause histologic chorioamnionitis actually reside in the uterus before the pregnancy. Korn and colleagues [111] observed in 1995 that nonpregnant women who had bacterial vaginosis were nearly ten times more likely to have bacterial vaginosis-associated organisms residing in the uterus than were women who did not have bacterial vaginosis. These women were far more likely to have an associated chronic plasma cell endometritis. Andrews and coworkers [112] also observed a large number of bacterial vaginosis related organisms in the uterus in healthy nonpregnant women. These data suggest that there are women who have their endometrium colonized with bacteria before pregnancy. These women are,

for the most part, asymptomatic, and would probably remain so until pregnant, because these colonizations do not seem to cause much in the way of symptoms, do not hinder conception to any large degree, and have little impact on the pregnancy until the second trimester. It has been hypothesized by the authors' group [71,86] that once the membranes become tightly applied to the decidua, essentially forming an abscess, only then do these colonizations become symptomatic. With the adherence of the membranes to the decidua at about 20 weeks' gestation, the inflammatory process accelerates, ultimately leading to a preterm birth, which usually occurs before 28 or 30 weeks' gestational age.

Bacterial vaginosis and preterm birth

Bacterial vaginosis (BV) is a vaginal syndrome associated with an alteration of the normal vaginal flora, rather than an infection specific to any one microorganism. BV is diagnosed clinically by the Amsel criteria, which include: (1) the presence of clue cells, (2) a pH higher than 4.5, (3) a profuse whitish discharge, and (4) a fishy odor when that discharge is treated with potassium hydroxide (KOH) [113]. For research purposes, bacterial vaginosis is often defined by the Nugent criteria, whereby air-dried vaginal smears are Gram-stained, and are scored based on the number of lactobacillus (which tend to be low), and the presence of organisms that look like *Mobiluncus* and *Bacteroides*, which tend to be high [114]. A score of 7 to 10 has traditionally been used to diagnose BV; however, a recent study [115] suggests that only the very highest scores (ie, 9 and 10) may be associated with preterm birth.

Nevertheless, BV diagnosed by a score of 7 to 10 has been associated with a one and a half- to threefold increased risk of preterm birth in more than 20 studies [116–118]. Therefore, there is more evidence for this association than for most epidemiologic associations reported in the literature. Interestingly, black women are considerably more likely to have BV than white women [119]. Though not explained by different rates of sexual intercourse or feminine hygiene practices, this two- to threefold difference may explain part of the racial differences in spontaneous preterm birth [120]. In fact, nearly 50% of the excess preterm births and preterm-associated mortality in black versus white infants may be explained by the increase in vaginal and intrauterine infections. Importantly, from a mechanistic point of view, women who have large quantities of these bacteria in the vagina appear more likely to have the same bacteria in the uterus associated with histologic chorioamnionitis. Gravett and colleagues [91], Silver and coworkers [121], Watts and colleagues [98], Hillier and colleagues [122], Krohn and coworkers [123], and others have all shown that there is an association linking BV and subsequent amnionitis, often with similar organisms. The mechanism by which BV is associated with amnionitis and preterm birth is uncertain, but it likely is the result of ascension of the vaginal organisms into the uterus either before, or early in, the pregnancy.

Sexually transmitted diseases and preterm birth

One of the difficult questions to answer related to genital tract infections with gonorrhea, chlamydia, trichomonas, group B streptococcus, and other organisms is whether they are causally associated with preterm birth. With virtually each of these organisms, a range of associations has been reported, varying from none to a strong relationship with preterm birth. In total, it appears that spontaneous preterm birth (defined as a birth following labor or rupture of the membranes) occurs more frequently in women who have and infection than in those who do not; however, even though gonorrhea, chlamydial infection, and other sexually transmitted diseases are usually found more frequently in women who have a spontaneous preterm birth, these women often have other risk factors as well. Furthermore, most studies claiming an association between various infections and preterm birth have not considered many of these confounding variables. As an example, gonorrhea has been associated with spontaneous preterm birth in a number of studies [124]. Almost none of these adjusted for most risk factors and especially for the presence of BV [125]. Therefore, although it is likely that maternal gonorrhea infection is associated with an independent two- or threefold risk for spontaneous preterm birth, this conclusion is not certain. As opposed to the organisms associated with BV, the gonococcus is rarely found in the amniotic fluid or the fetal membranes in women who give birth prematurely. Syphilis is widely reported to be associated with a twofold increased risk of preterm birth, and this relationship is relatively consistent in most studies [126].

Chlamydial infection has been associated with prematurity in some studies but not in others, with the majority of the studies showing no increased risk [118,127]. Sweet and coworkers [128], however, reported that women who had *Chlamydia trachomatis* infection and IgM antibodies were more likely to have a spontaneous preterm birth compared with women who have chlamydia infection and IgG, but not IgM, antibodies. In the Preterm Prediction Study [129], women tested for *Chlamydia trachomatis* at 24 weeks' gestation had about twice as many preterm births associated with the presence of this organism as did uninfected women; however, after adjusting for other risk factors, this association was no longer significant, contributing to the continuing uncertainty about whether chlamydia infection plays a causative role in preterm birth. Many of the other sexually transmitted diseases, such as HIV, hepatitis B, and genital herpes simplex virus, have been associated with an increased risk for spontaneous preterm birth in some, but not most, studies. In general, the evidence for a causative link between maternal infection with these organisms and spontaneous preterm birth is poor [75].

Non–genital tract infections and preterm birth

Several non–genital tract infections seem to be related to, and are probably causal for, preterm birth. The first of these is urinary tract infection. In a meta-analysis of the existing literature by Romero and colleagues [164], urinary tract

infection was clearly associated with preterm birth, and antibiotic treatment of urinary tract infection did result in a reduction of preterm birth. Maternal pneumonias and other systemic infections such as appendicitis also appear to increase the risk of preterm birth. Recently, research efforts have focused on exploring the relationship between maternal periodontal disease and subsequent preterm birth [110,130]. This association has now been confirmed at several study sites. Importantly, recent evidence suggests that treatment of the periodontal disease with deep cleaning, as opposed to the use of antibiotics, may reduce the associated preterm birth [131].

Viral infections and preterm birth

In comparison with bacterial infections, the evidence that viral infections are causal for preterm birth is quite sparse; however, in cases of viral infection when the mother has a severe systemic illness, such as varicella pneumonia or polio, a preterm delivery may occur [22,23]. Recent reports suggest that a maternal infection with the severe acute respiratory syndrome (SARS) virus can result in preterm birth as well [132]. In the absence of major systemic disease, the evidence for a relationship between maternal viral infection and preterm delivery is based mostly on case reports. For example, a number of fetuses that had an intrauterine CMV infection have been noted to deliver preterm, although the denominator for such observations is unknown. In the several studies in which asymptomatic women undergoing genetic amniocentesis were evaluated for intraamniotic viral infection using PCR techniques, a number of different viral DNAs were identified in the amniotic fluid, but their presence was not related to subsequent preterm birth [133]. Therefore, it seems unlikely that maternal viral infection plays an important role in preterm birth. Because of the limited information available, however, further study of this potential relationship is in order.

Maternal infections and the types of adverse pregnancy outcomes

Based on the authors' review of the literature, Table 2 [76,134–136] presents a summary of the types of adverse perinatal outcomes that have been associated with specific maternal infections.

Many of the infants infected with a specific organism during fetal life or during delivery and who manifest disease, do so in the neonatal period. These include most of the infants infected with herpes simplex virus, syphilis, and gonorrhea; however, for many others, the disease will not become apparent for months or years later. For example, although the ophthalmologic damage caused by *Neisseria gonorrhoeae* and *C trachomatis* becomes apparent within several days or weeks after birth, the pneumonia associated with chlamydia infection may occur months after delivery [137,138]. The deafness associated with neonatal cytomegalovirus is often not apparent until later in childhood, and the

Table 2
Adverse reproductive outcomes associated with maternal infection

Maternal colonization/ organism	Infertility	Abortion	Congenital anomalies	Stillbirth	IUGR
Bacterial vaginosis	–	–	–	–	–
Chlamydia	+	–	–	–	–
Coxsackievirus	–	–	±	+	–
Cytomegalovirus	–	–	–	–	+
Echovirus	–	–	–	±	–
Gonorrhoea	+	–	–	–	–
Group B streptococcus	–	–	–	+	–
Hepatitis B	–	–	–	–	–
Hepatitis C	–	–	–	–	–
Herpes simplex	–	–	–	–	–
HIV	–	–	–	–	±
HPV	–	–	–	–	–
Influenza	–	+	–	±	–
Listeria	–	+	–	+	+
Lyme borreliosis	–	–	–	+	+
Malaria	–	+	–	+	+
Measles	–	–	–	–	+
Mumps	+	±	–	±	–
Parvovirus	–	+	–	+	–
Rubella	–	±	+	+	+
SARS	–	+	–	+	±
Syphilis	–	+	+	+	+
Toxoplasmosis	–	+	–	+	+
Trichomonas	–	–	–	–	–
Tuberculosis	–	–	–	±	–
Varicella	–	–	+	±	+

–, Occurs rarely if at all; +, established relationship; ±, may occur, uncommon.
Data from Refs. [75,134–136].

neurological sequelae of fetal or neonatal infections with toxoplasmosis, CMV, rubella, herpes virus, Group B streptococcus and syphilis are often not apparent until later as well [40,139]. The most important outcome in HIV-infected neonates, childhood acquired immunodeficiency syndrome (AIDS), does not usually appear until after infancy. The chronic hepatitis resulting from perinatal infection with the hepatitis B virus is usually not symptomatic in the neonatal period, and the late sequelae of perinatal hepatitis B infection, including cirrhosis and hepatocellular carcinoma, generally occur decades later [140,141]. Congenital infection with the human papilloma virus has been implicated in laryngeal papillomas and several childhood cancers [142,143].

Prevalence and the timing of transmission

There are many definitions of ‘‘prenatal,’’ ‘‘perinatal,’’ and ‘‘intrapartum’’ in use today. In the following discussion, prenatal refers to the period between

Preterm birth	Neonatal death	Postnatal disease	Long-term disability		
			Deafness	Eye disease	Neurologic
+	−	−	−	−	−
+	−	+	−	+	−
−	−	−	−	−	±
+	+	+	+	+	+
−	+	−	−	−	−
+	−	−	−	+	−
−	+	+	−	−	+
−	−	+	−	−	−
−	−	+	−	−	−
−	+	+	−	+	+
±	−	+	−	−	±
−	−	+	−	−	−
+	−	−	−	−	−
+	+	+	−	−	+
±	−	−	−	−	±
±	−	−	−	−	−
+	+	+	−	−	−
−	−	−	−	−	−
−	−	−	−	−	−
−	+	+	+	+	+
±	−	−	−	−	−
+	+	+	+	−	+
−	−	−	−	+	+
+	−	−	−	−	−
−	+	+	−	−	−
+	+	+	−	+	+

conception and the events leading to delivery, perinatal refers to the time between the onset of labor or rupture of membranes and approximately 1 month after delivery, and intrapartum refers to the period between the onset of labor and delivery. The numerical values used for infection and transmission rates and the percentage of infected infants who had various sequelae used in the following tables are based on a wide variety of sources with widely discrepant estimates [76,134]. These differences may reflect differences in study design, laboratory methodology, or population differences (race and socioeconomic status or size of study population), or case definition.

Table 3 describes the maternal prevalence of a number of infections, as well as the timing of transmission and the percent of neonates infected when the mother is colonized. For example, syphilis, hepatitis B, and HIV infections are currently found in approximately 0.10% to 0.2% of pregnant women in the United States [144,145]. Gonorrhea infections are found in about 1% of all pregnant women, and trichomonas and chlamydia in about 5% [146–148]. Maternal colonization with herpes simplex virus, and bacterial vaginosis is found in approximately 20%

Table 3
Perinatal transmission of major human pathogens

Maternal infection/ organism	Approximate maternal prevalence (%)	Usual timing of transmission		Neonates infected/ colonized (%) when mother colonized and not treated
		Prenatal	Intrapartum	
Bacterial vaginosis	20.0	–	–	0
Chlamydia	5.0	–	+	50.0
Coxsackievirus	1.0	+	–	±
Cytomegalovirus	33.0[a]	+	+	3.0
Echovirus	Variable	–	+	±
Gonorrhoea	1.0	–	+	50.0
Group B streptococcus	20.0	±	+	50.0
Hepatitis B	0.2	–	+	30.0
Hepatitis C	2.0	–	+	8
Herpes simplex	20.0[a]	±	+	0.2
HIV	0.2	+	+	25.0
HPV	5.0	–	+	5.0
Influenza	Variable	+	–	±
Listeria	Rare	+	–	±
Lyme borreliosis	0.1	+	–	±
Malaria	Variable	+	–	4.0
Measles (rubeola)	Rare	+	–	±
Mumps	Rare	+	–	±
Parvovirus	1.0	+	–	20.0
Rubella	Rare	+	–	50.0
Syphilis	0.12	+	±	40.0
Toxoplasmosis	1.0	+	–	30.0
Trichomonas	5.0	–	–	0
Tuberculosis	Rare	+	–	±
Varicella	Rare	+	+	2.0

+, Established relationship; ±, may occur, uncommon; –, occurs rarely if at all.
[a] By serology.
Data from Refs. [75,134–136].

of pregnant women. Cytomegalovirus infection is estimated to be present in about one third of all pregnant women [149,150].

Infants are virtually never infected with *Trichomonas.* Manifestation of bacterial vaginosis in the infant is unknown; however, neonatal infections with *U urealyticum*, *Mycoplasma hominis*, various bacterioides spp, *Gardnerella* or other bacterial vaginosis-related organisms have been reported, although rarely [151]. Congenital syphilis is usually transmitted after the first trimester, but can be transmitted at any time during the pregnancy or at delivery. *N gonorrhoeae, C trachomatis,* and the hepatitis B virus rarely infect the fetus in the prenatal period and are almost never found in the uterus before rupture of the membranes [1,74,124,152–154]. Instead, the fetus generally acquires these organisms as it passes through the birth canal. Fetal infections with herpes simplex virus rarely occur before the rupture of the membranes [155,156]. Instead, the vast majority

of transmissions occur after the rupture of the membranes or in the intrapartum period. Transmission rates to the fetus vary depending on whether the infection is primary or recurrent. Neonatal HIV infection may be acquired prenatally, but studies of second trimester abortuses suggest that early in utero infection is rare. Using a mathematical model, Rouzioux and colleagues [157] estimated that one third of the transmissions occur in the last 2 weeks of pregnancy and two thirds occur in the intrapartum period. Women who have an HIV infection and whose membranes rupture more than 4 hours before delivery or who are delivered vaginally are, in most studies, more likely to transmit this infection to their neonates [158–160].

If the mother is infected, variable percents of the exposed infants, depending upon the disease, become colonized (see Table 3). Without treatment, these rates of transmission range from 0.2% for herpes simplex, to 3% for cytomegalovirus, and up to 25% to 40% for syphilis, hepatitis B virus, and HIV [161]. If routine ophthalmic prophylaxis is not used, approximately 30% to 50% of the infants [52] of infected mothers acquire gonorrhea or chlamydia ophthalmic infections.

Transmission of organisms to the fetus and newborn

Because the influence of maternally transmitted organisms on adverse outcomes of pregnancy are generally presented in individual papers, it may be instructive to compare their impact. For a subset of maternal infections that are associated with fetal infection, Table 4 indicates not only the maternal and infant prevalences in the 4 million births per year in the United States, but also the approximate number of mothers and infants who have an infection. Also displayed in this table is the approximate number of infants each year in the United States who have specific types of sequelae associated with direct fetal or infant infection. The potential excess in preterm births attributable to various infections and the sequelae associated with those preterm births are discussed later. When translated into the total US population, this means that there are approximately 4000 to 8000 pregnant women per year who have syphilis, hepatitis B, or HIV; about 40,000 pregnant women per year infected with gonorrhea; about 80,000 pregnant women who have *Trichomonas*; perhaps 200,000 pregnant women who have chlamydia; and approximately 800,000 pregnant women per year who have herpes simplex virus or BV. It is estimated that approximately 1.3 million pregnant women are infected/colonized with CMV. Again, these numbers are our best estimates for infection for the entire population of pregnant women who give birth in the United States each year. Subpopulations of women who have markedly higher and lower prevalences have been described. For both herpes simplex virus and cytomegalovirus, it is assumed that previous infection, as defined serologically, is associated with persistent infection.

Table 4
The estimated impact of direct fetal and neonatal infection with various infections on adverse outcomes of pregnancy each year in the 4,000,000 United States births

Maternal infection/ organism	Approximate maternal prevalence (%)	Mothers infected/ colonized (no.)	With current treatment in the United States, of infected mothers, % and no. of infants colonized		Adverse outcomes of fetal neonatal infection/colonized			
			%	No.	Neonatal disease without sequelae	Perinatal death	Neurologic sequelae	New onset post-neonatal illness and death
Bacterial vaginosis	20.0	800,000	0	0	0	0	0	0
Chlamydia[a]	5.0	200,000	50.0	100,000	20,000[b]	0	0	0
Cytomegalovirus	33.0	1,300,000	3.0	40,000	±	300	2000	5000[c]
Gonorrhea[a]	1.0	40,000	50.0	20,000	±	±	±	0
Group B streptococcus[d]	20.0	800,000	12.5	100,000	1200	150	150	—
Hepatitis B[e]	0.2	8000	10.0	800	0	0	0	300
Herpes simplex	20.0	800,000	0.15	1200	400	400	400	0
HIV[f]	0.2	8000	1.0	80	0	0	0	80
Rubella	Rare	—	—	—	0	0	0	0
Syphilis	0.12	4800	40.0	1920	720	720	600	0
Trichomonas	5.0	200,000	0	0	0	0	0	0

±, Occurs, but rarely.

[a] Assumes prophylaxis for eye disease.

[b] Mild pneumonia.

[c] Hearing loss.

[d] Assuming current screening and treatment programs reduce transmission by 75% and that 1.5% of colonized infants develop sepsis.

[e] Assuming current screening and treatment programs reduce transmission by 70%.

[f] Assuming current screening and treatment programs reduce transmission to 1%.

Data from Refs. [75,135,136].

Adverse outcomes associated with perinatal transmission

The next several columns in Table 4 show potential outcomes associated with fetal and perinatal infection with each of the organisms. These are estimates of outcomes achieved in the United States with current medical practices. From the existing literature, it is estimated that of the 1920 infants infected with syphilis at the time of birth, approximately 600 will be stillborn or will die as neonates, and about 600 will have long-term neurological or other sequelae. Approximately 720 of these 1920 infants will live and not have apparent long-term sequelae. With gonorrhea, assuming no ophthalmologic disease because of prophylaxis, there will be few major sequelae in the infant from neonatal infection. Of the 100,000 infants infected with chlamydia at birth, again assuming no long-term ophthalmologic sequelae because of prophylaxis, it is estimated that there will be approximately 20,000 cases of chlamydial pneumonia, nearly all of which will regress spontaneously or respond to antibiotics and not result in long-term sequelae or death [135]. Without immunoprophylaxis, of the 12,000 infants infected with hepatitis B virus at birth, approximately 4000 will ultimately develop cirrhosis or hepatocellular carcinoma [140,162]. These numbers should be substantially reduced with routine neonatal hepatitis B immunoglobulin prophylaxis and vaccination, and although the numbers are unknown, the authors estimate that about 300 will develop cirrhosis or hepatocellular carcinoma sometimes in their lives. Of the 1200 infants infected at birth with herpes simplex virus, an estimated 400 will die during the perinatal period, approximately 400 will have neurological sequelae, and 400 will have neonatal disease but no long-term sequelae. Of the 40,000 infants infected with CMV, approximately 7% will have signs of disease in the neonatal period. Of these 2800 infants, some 300 will die, whereas 2000 more will have major neurological sequelae. Newell [163] estimates that as much as 7% of all cases of cerebral palsy are due to CMV infections. Later in life, an additional 5000 infants will have significant hearing loss associated with the CMV infection [147]. As stated above, it is estimated that with maternal and infant prophylaxis, fewer than 100 infants per year in the United States will be infected with HIV. It is assumed that even with treatment, each of these infants will ultimately manifest AIDS and die of the disease.

Adverse outcomes associated with infection-related preterm birth

As discussed above, it is not absolutely clear whether maternal infections such as gonorrhea, syphilis, chlamydial infection, Group B streptococcal infection, or trichomoniasis result in preterm birth. The data supporting the association of BV with spontaneous preterm birth are more solid. Although the relationships are uncertain, based on the authors' assessment of the literature, we assumed that gonorrhea is associated with a threefold increase in the preterm birth rate, and that syphilis and chlamydial infection are associated with a twofold increase in pre-

Table 5
The estimated impact of various infections on adverse outcomes of pregnancy[a] through their effect on preterm birth

Maternal infection/ organism	Approximate maternal prevalence (%)	Mothers infected (no.)	Estimated increase in preterm birth[b] (×)	Estimated excess preterm birth[c] (no.)	Adverse outcomes linked to preterm birth[d]	
					Perinatal death (no.)	Neurologic sequelae (no.)
Bacterial vaginosis	20.0	800,000	2×	80,000	4000	4000
Chlamydia	5.0	200,000	2×	20,000	1000	1000
Cytomegalovirus	33.0	1,300,000	[e]	—	—	—
Gonorrhea	1.0	40,000	3×	8000	400	400
Group B streptococcus	20	80,000	[e]	—	—	—
Hepatitis B	1.0	40,000	[e]	—	—	—
Herpes simplex	20.0	800,000	[e]	—	—	—
HIV	0.2	8000	[e]	—	—	—
Rubella	0	0	[e]	—	—	—
Syphilis	0.12	4800	2×	480	24	24
Trichomonas	2.0	80,000	1.3	2400	120	120

[a] Assuming 4,000,000 births per year.
[b] Based on best available data in untreated women.
[c] Assuming a baseline preterm rate of 10%.
[d] Assuming 5% deaths and 5% neurologic sequelae.
[e] Insufficient evidence for a causative relationship.

Data from Refs. [75,135].

term birth. Bacterial vaginosis is associated with a twofold increase and trichomonas with a 1.3-fold increase. From these numbers and the rates of maternal infection, assuming a 10% rate of prematurity in the general population, the excess number of preterm births per year in the United States associated with maternal infection with each organism can be calculated (Table 5). As an example, if 40,000 pregnant women in the Unites States are infected per year with gonorrhea, and if these women have a 30% instead of a 10% rate of spontaneous preterm birth, maternal gonorrhea infection may be associated with an estimated 8000 excess preterm births. Of the 4800 women who have syphilis, assuming a twofold increase in preterm birth, approximately 480 excess preterm births due to syphilis may occur in the United States each year. Assuming a twofold increase in preterm birth, with 200,000 mothers having chlamydial infection each year, as many as 20,000 excess preterm births may be associated with maternal chlamydial infection. Applying this same logic to maternal BV infections and assuming a twofold increase in preterm birth associated with BV, of the 800,000 women who have BV, an excess of 80,000 preterm births may occur.

The last two columns in Table 4 show the estimated number of perinatal deaths and infants who have major neurological handicaps associated with maternal infections and preterm birth, if it is assumed that 5% of the preterm infants die and 5% are neurologically handicapped with such conditions as blindness, hydrocephalus, mental retardation, or cerebral palsy. If these assumptions are correct, prematurity secondary to maternal gonococcal infections may be responsible for approximately 400 perinatal deaths and 400 children experiencing long-term neurological sequelae. Through its influence on preterm birth, syphilis would be responsible for an additional 16 perinatal deaths and for 16 children who have long-term neurological sequelae. Through its impact on preterm birth, chlamydial infection might account for as many as 1000 excess perinatal deaths and 1000 children who have long-term disability. Maternal BV, because of its high prevalence in the population and an associated twofold increase in preterm birth, may be responsible for approximately 80,000 excess preterm births, 4000 perinatal deaths, and 4000 children who have long-term neurological sequelae. The authors emphasize that most of these adverse outcomes associated with preterm birth occur without apparent fetal or neonatal infection.

Summary

Fetal or neonatal infections with the agents of sexually transmitted diseases—syphilis, herpes simplex virus, and HIV —ay have a devastating effect, including either death or long-term neurological disability. In the United States, associated with each of these infections, between 1000 and 2500 infants per year die or are severely damaged. In contrast to these relatively rare outcomes, approximately 400,000 infants are born prematurely each year, and of these, more than 20,000

die in the fetal or the neonatal period, and another 20,000 have neurological sequelae. If the projected effect on preterm birth by BV and the other organisms proposed here is correct, as many as 100,000 preterm births and 5000 or more of the deaths, as well as a similar number of the major disabilities, may be associated with maternal infections. Because some studies suggest that some of the preterm births associated with BV and intrauterine infection may be prevented, it seems that the greatest potential for reducing adverse outcomes of pregnancy associated with maternal infection lies in preventing or treating BV and intrauterine infection-associated preterm births.

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