The infectious origins of stillbirth

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OBJECTIVE: Our objective was to determine the relationship between various types of perinatal infections and stillbirths.

STUDY DESIGN: By use of various textbooks on perinatal infections, multiple MEDLINE searches, and the reference list of all appropriate manuscripts, the appropriate English language literature was reviewed to define the relationship between various perinatal infections and stillbirths.

RESULTS: Infection may cause stillbirth by a number of mechanisms, including direct infection, placental damage, and severe maternal illness. A large variety of organisms have been associated with stillbirth, including many bacteria, viruses, and protozoa. In developed countries, between 10% and 25% of stillbirths may be caused by an infection, whereas in developing countries, which often have much higher stillbirth rates, the contribution of infection is much greater. Ascending bacterial infection, both before and after membrane rupture, with organisms such as Escherichia coli, group B streptococci, and Ureaplasma 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.

CONCLUSION: Because infection-related stillbirth is relatively rare in developed countries, and those that do occur are caused by a wide variety of organisms, reducing this etiologic component of stillbirth much further will be difficult. However, in certain developing countries, the stillbirth rate is so high and the infection-related component so great that achieving a substantial reduction in stillbirth should be possible simply by reducing maternal infections. (Am J Obstet Gynecol 2003;189:861-73.)

Key words: Stillbirth, infection, chorioamnionitis

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.1 As with most other adverse pregnancy outcomes, African American women have a greater (2-fold) risk of stillbirth than white women do.5 Stillbirth occurs far more frequently in developing countries than developed countries, with rates as high as 90:1000 reported in some areas.8 In many countries, especially the most developed ones, over the last several decades there has been a significant reduction in stillbirths. Much of this decrease has occurred in term or near-term stillbirths and is mostly due to improvements in medical care.4,5

Stillbirths are frequently categorized by presumed etiology. Important noninfectious causes of stillbirth include congenital anomalies, asphyxia related to pre-eclampsia, abruptio placenta, and umbilical cord accidents.6-10 Maternal and fetal trauma, maternal obesity, low education, smoking, fetal growth restriction, advanced maternal age, Rh disease, and diabetes mellitus are risk factors for stillbirth. More than half the cases of stillbirth are associated with or caused by one or more of these conditions. A smaller, but unknown, percentage of stillbirths may be caused by various types of maternal or fetal infections.11,12

Definition of stillbirth

The lower limits of gestational age and birth weight that have been used to distinguish a second-trimester spontaneous abortion from a stillbirth have varied widely, both in official definitions and across studies.13 Definitions have
included lower gestational age limits ranging from 20 to 28 weeks and from 350 to 1000 g birth weight. Because infection is more clearly associated with early compared with late stillbirths, studies that only evaluate later fetal deaths, such as those occurring after 28 weeks, will likely not find as strong a relationship with infection as those that evaluate all fetal deaths from 20 or 22 weeks onward. For example, a Canadian study found that 19% of stillbirths at less than 28 weeks were associated with infection, whereas at term only 2% were attributed to infection. Similar results were found in Alabama.

For example, a Canadian study found that 19% of stillbirths at less than 28 weeks were associated with infection, whereas at term only 2% were attributed to infection. Similar results were found in Alabama. Therefore, for the purposes of this review, whenever possible, a stillbirth will be defined by the most common US definition, which is a fetal death occurring at greater or equal to 20 weeks’ gestation. Stillbirths are traditionally divided into three categories: early preterm, typically using 28 weeks or 1000 g as a cutoff value; late preterm, 28 to 36 weeks; and those occurring at term, 37 weeks and more. Death itself is defined as having no sign of life, such as a heartbeat or spontaneous respiration, after delivery. Consistent with the definition above, the terms stillbirth, fetal death, and intrauterine fetal death will be used interchangeably.

**Infection and stillbirth**

For a number of reasons, the relationship between maternal infection and stillbirth is often not very clear. 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.

Conceptually, infection may result in fetal death through many different pathways. First, a maternal infection may lead to a systemic illness where 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. 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. Third, the fetus may be directly infected through the placenta or membranes, with the infectious organisms damaging a vital fetal organ such as the lung, liver, heart, or brain. Examples of this type of infection include the fetal pneumonia associated with *Escherichia coli* or group B streptococcal chorioamnionitis or the systemic infections with viruses such as coxsackie A or B.

If an infection occurs very early in gestation, the fetus may not die but may have a congenital anomaly with a fetal death occurring later, as a result of the anomaly. Rubella infection has been associated with stillbirths by this mechanism. And last, 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. *Ureaplasma* 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 nongenital 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.

From the examples noted above, and others that will be provided later in this review, it is obvious that stillbirths have been reported in association with virtually all types of infection, including those caused by bacteria, viruses, and many different types of parasites. Nevertheless, it is important to note that of the thousands of infectious agents in the environment, only a relatively small number have ever been transmitted to the fetus or have been associated with stillbirth.

**Specific infections related to stillbirth (Table)**

**Spirochete infections.** *Treponema pallidum*, the spirochete responsible for syphilis, is transmitted between adults mainly through sexual contact. In US women of childbearing age, the overall prevalence of primary and secondary syphilis in 1999 was 2.5 per 100,000, substantially less than the 17.3 per 100,000 women in 1990. In Russia, in recent years, the prevalence of syphilis was reported as high as 175 per 100,000 women. Syphilis may be far more prevalent in some developing countries, with rates of 10% to 20% (10,000-20,000 per 100,000) reported in some populations of African pregnant women.

Syphilis may be transmitted to the fetus transplacentally, causing congenital syphilis. In 1991, there were 107.3 cases of congenital syphilis per 100,000 live births,
but this rate has fallen substantially, to 13.4 cases per 100,000 births in 1999. Spirochetes are able to cross the placenta and infect the fetus at 14 weeks’ gestation, and perhaps earlier, with risk of fetal infection increasing with gestational age. If the fetus is infected, about 40% to 50% will die in utero, with another 30% to 40% being born alive but having signs of congenital syphilis. The most common cause of fetal death appears to be placental infection associated with decreasing blood flow to the fetus, although direct fetal infection also plays a role. In a recent study of 33 stillbirths in which syphilis was the likely causal agent, placental histopathologic study revealed villous enlargement, acute villitis, erythroblastosis, and necrotizing funisitis indicative of a fetal vasculopathy.

With syphilis now so rare in most developed countries, it barely contributes to the stillbirth rate. However, in southern Africa, where 10% or more of pregnant women

<table>
<thead>
<tr>
<th>Organism</th>
<th>Maternal disease</th>
<th>Comment</th>
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<tr>
<td>Spirochetes</td>
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<tr>
<td><em>Treponema pallidum</em></td>
<td>Syphilis</td>
<td>Major cause of stillbirth when maternal prevalence is high</td>
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<tr>
<td><em>Borrelia burgdorferi</em></td>
<td>Lyme disease</td>
<td>Confirmed relationship but not common cause of stillbirth</td>
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<tr>
<td><em>Borrelia recurrentis</em></td>
<td>Tick-borne relapsing fever</td>
<td>Rarely associated, of unknown importance as cause of stillbirth</td>
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<td><em>Leptospira interrogans</em></td>
<td>Leptospirosis</td>
<td>Confirmed as cause of stillbirth but not common</td>
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<td>Protozoa</td>
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<tr>
<td><em>Trypanosoma brucei</em></td>
<td>Trypanosomiasis</td>
<td>Not certain cause of stillbirth</td>
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<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>Chagas disease</td>
<td>Confirmed as cause of stillbirth in South America but of unknown importance</td>
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<tr>
<td><em>Plasmodium falciparum, Plasmodium vivax</em></td>
<td>Malaria</td>
<td>Likely important cause of stillbirth in newly endemic areas or in newly infected women</td>
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<tr>
<td><em>Toxoplasmosis gondii</em></td>
<td>Toxoplasmosis</td>
<td>Confirmed as cause of stillbirth but not common</td>
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<td><em>Coxiella burnetii</em></td>
<td>Q fever</td>
<td>Confirmed as cause of stillbirth but of unknown importance</td>
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<td>Viruses</td>
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<tr>
<td>Parvovirus (B19)</td>
<td>Erythema infectiosum</td>
<td>Confirmed as cause of stillbirth, likely most common viral etiologic agent</td>
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<tr>
<td><em>Coxackie A and B</em></td>
<td>Various presentations</td>
<td>Confirmed as causes of stillbirth, may be important contributor</td>
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<td><em>Echovirus</em></td>
<td>Various presentations</td>
<td>Confirmed as cause of stillbirth but of unknown importance</td>
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<tr>
<td><em>Enterovirus</em></td>
<td>Various presentations</td>
<td>Confirmed as cause of stillbirth but of unknown importance</td>
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<tr>
<td><em>Polio virus</em></td>
<td>Polio</td>
<td>Historically likely cause of stillbirth but since routine vaccination no longer seen in developed countries</td>
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<tr>
<td><em>Varicella zoster</em></td>
<td>Chickenpox</td>
<td>Confirmed as cause of stillbirth but not common</td>
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<tr>
<td><em>Rubella</em></td>
<td>German measles</td>
<td>Confirmed, but no longer cause of stillbirth in developed countries</td>
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<tr>
<td>Mumps</td>
<td>Parotitis</td>
<td>Possibly cause of stillbirth historically but no longer cause of stillbirth in developed countries</td>
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<td>Rubeola</td>
<td>Measles</td>
<td>Possibly cause of stillbirth historically</td>
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<tr>
<td>Cytomegalovirus</td>
<td>Generally asymptomatic in adults</td>
<td>Rarely if ever cause of stillbirth</td>
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<tr>
<td>Varioi</td>
<td>Smallpox</td>
<td>Historically cause of stillbirth but no longer seen</td>
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<tr>
<td><em>Lymphocytic choriomeningitis virus</em></td>
<td>Lymphocytic choriomeningitis</td>
<td>Not confirmed as cause of stillbirth, of unknown importance</td>
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<td><em>Human immunodeficiency virus</em></td>
<td>Acquired immunodeficiency syndrome</td>
<td>Associated with stillbirth but not likely causative</td>
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<tr>
<td>Bacteria</td>
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<tr>
<td><em>E. coli</em></td>
<td>Generally asymptomatic</td>
<td>Confirmed, probably the most common organism associated with stillbirth</td>
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<tr>
<td><em>Group B Streptococcus</em></td>
<td>Generally asymptomatic</td>
<td>Confirmed as common cause of stillbirth</td>
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<tr>
<td><em>Klebsiella</em></td>
<td>Generally asymptomatic</td>
<td>Confirmed, common cause of stillbirth</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Generally asymptomatic</td>
<td>Confirmed</td>
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<tr>
<td><em>U. urealyticum</em></td>
<td>Generally asymptomatic</td>
<td>Confirmed</td>
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<tr>
<td><em>Mycoplasma hominis</em></td>
<td>Generally asymptomatic</td>
<td>Confirmed</td>
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<tr>
<td><em>Bacteroidaceae</em></td>
<td>Generally asymptomatic</td>
<td>Confirmed</td>
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<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Listerosis</td>
<td>Confirmed, generally transmitted transplacentally</td>
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<tr>
<td><em>Other bacteria including brucellosis, Clostridia, Agrobacterium radio-bacter, Pseudomonas, etc</em></td>
<td>Pelvic infection</td>
<td>Potentially implicated as causal for stillbirth by case reports</td>
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<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>Pelvic infection</td>
<td>Suggested as cause of stillbirth by case reports</td>
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<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Pelvic infection</td>
<td>Suggested as cause of stillbirth by case reports</td>
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<td>Fungi</td>
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<tr>
<td><em>Candida albicans</em></td>
<td>Thrush, vaginitis</td>
<td>Confirmed as cause of stillbirth by case reports</td>
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are often seropositive, between 25% and 50% of all stillbirths are found in seropositive women, and at least 25% of all stillbirths are attributed to this infection.\textsuperscript{25-28} For example, Folgosa et al\textsuperscript{26} found a positive specific serologic test for syphilis in 42% of stillbirths versus only 12% of controls. In a study in Zambia, 42% of the mothers of stillbirths also had syphilis versus 12% of controls.\textsuperscript{28} In a study in Bolivia, 26% of mothers of stillborn infants had syphilis versus 4.3% of controls.\textsuperscript{31} Interestingly, in 1917, Osler estimated that 20% of US stillbirths occurred as a result of syphilis.\textsuperscript{24}

Syphilis is not the only spirochetal infection that is associated with stillbirth. In recent years, Lyme disease, a systemic illness caused by the tick-borne spirochete \textit{Borrelia burgdorferi} also has been shown to cause stillbirth.\textsuperscript{32} The first cases of perinatal transmission were described in the mid 1980s,\textsuperscript{33-36} and the first case of stillbirth associated with Lyme disease was described in 1987.\textsuperscript{35} In the latter case, the mother acquired the disease in the first trimester, and at 34 weeks was delivered of a stillborn infant who at autopsy had \textit{B burgdorferi} in the placenta and in internal fetal organs. In other reports, after first-trimester infection and subsequent fetal death, spirochetes have been found in fetal liver, spleen, kidney, hepatic vein lumen, and brain tissue. Subsequently, small series of stillbirths after maternal Lyme disease have been described, with most deaths occurring in the mid trimester. However, larger-scale serologic studies have shown that, except in highly endemic areas, few stillbirths are associated with Lyme disease.\textsuperscript{37} In endemic areas in the United States and Norway, the seropositive rate in pregnant women is 2% or less. Interestingly, there is a report from Tanzania that the \textit{B burgdorferi} seropositive rate is more than 30%.\textsuperscript{38} The implications for pregnancy outcome in Tanzanian women are unknown.

Another spirochetal disease associated with adverse pregnancy outcome is African tick-borne relapsing fever. One study reported a perinatal mortality rate of 30% with maternal infection and described the isolation of spirochetes from the placenta.\textsuperscript{39} The contribution of this disease to the overall stillbirth rate in endemic areas in Africa is unknown. Leptospirosis, still another spirochetal disease, has also been associated with transplacental infection and stillbirth.\textsuperscript{40,41}

Although not a spirochetal disease, trypanosomiasis, better known as African sleeping sickness and transmitted by the tsetse fly, has been associated with stillbirth.\textsuperscript{42} The parasites, \textit{Trypanosoma brucei}, have been demonstrated in the placentas of dead fetuses. How commonly this occurs is unknown. Another trypanosomal illness, Chagas disease, caused by \textit{Trypanosoma cruzi}, is widespread in South America and may infect the fetus and placenta, causing hydrops and death.\textsuperscript{11,43} As with African sleeping sickness, the extent to which maternal infection is linked to stillbirth is unknown.

Malaria. Malaria, one of the world’s largest health problems, is caused by one of four types of intracellular parasites (especially \textit{Plasmodium falciparum} and \textit{Plasmodium vivax}) transmitted by various types of mosquitoes. More than 40% of all births worldwide occur in areas with endemic malaria.\textsuperscript{44} Because pregnant women appear to be more susceptible to the effects of malaria than other adults, malaria is associated with a wide range of adverse pregnancy outcomes, but especially growth restriction and preterm birth.\textsuperscript{45} In endemic areas, malaria approximately doubles the maternal risk of moderate to severe anemia, triples the risk of preterm birth, and perhaps quadruples the risk of fetal growth restriction.\textsuperscript{46-49} However, the effect of malaria on stillbirth has rarely been studied. The impact of malaria on pregnancy outcomes varies based on the type of malaria (\textit{P falciparum} is worst), the mother’s parity, and her immune status. For example, in primigravid women living within endemic areas, placental malaria has been reported to occur in 16% to 63% of maternal infections.\textsuperscript{44} In multigravida women, 12% to 33% of infected mothers have placental malaria. With a maternal malaria infection, the pregnancy outcome is directly related to the extent of placental malaria, and in part to the degree of maternal anemia. Histologically, placental malaria is characterized by parasites and leukocytes in the intervillous space and pigment within macrophages.\textsuperscript{16,45} When the parasites infect the placenta, placental insufficiency often results because of lymphocyte and macrophage accumulation, thickening of the trophoblast basement membrane, and increased expression of various proinflammatory cytokines, all of which impede maternal blood flow through the placenta.\textsuperscript{50,51} This leads to restricted transport of oxygen and nutrients to the fetus. Placental malaria infection also apparently decreases antibody transfer across the placenta, increasing susceptibility to conditions such as neonatal tetanus.\textsuperscript{52} Also, malaria organisms do cross the placenta, and congenital malaria, although not as common as placental infection, certainly occurs.

It is difficult to derive an attributable risk of stillbirth associated with malaria in most populations because the prevalence of malaria is high, malaria rarely exists in isolation from other risk factors, and finding evidence of malaria in the placenta of a stillbirth does not prove causation. However, Newman et al,\textsuperscript{53} in a recent report, found a 7-fold increased risk of stillbirth in an Ethiopian population newly infected with malaria. Their work suggests that in endemic areas where nearly everyone has had a number of malaria infections during childhood and a maternal immune response has developed, malaria infection during pregnancy is only minimally associated with stillbirth. However, in populations of pregnant women experiencing a malaria infection for the first time, malaria is likely an important cause of stillbirth.
**Toxoplasmosis.** *Toxoplasmosis gondii* is a parasite that normally spends its life cycle in animals such as cats. It is passed to humans through contact with animal feces or is ingested while eating raw or undercooked beef or pork. When toxoplasma infects adult humans, it typically causes a mild systemic illness. Past maternal infection, indicated by the presence of antibodies, indicates that the pregnant woman is at little or no risk for a fetal infection. Overall, toxoplasmosis seropositivity in the United States is about 15%, but in other populations the prevalence may be considerably higher. For example, among pregnant women in Nigeria, the prevalence of toxoplasma antibodies was more than 80%. In the United States and Scandinavia, the incidence of primary toxoplasmosis infection during pregnancy is 0.5 to 2.0 per 1000, and the prevalence of congenital toxoplasmosis in live-born children is reported at 7.3 per 100,000 births.

If the mother acquires the infection during pregnancy, toxoplasmosis may be transplacentally transmitted to the fetus. Maternal-fetal transmission is dependent on the time of maternal infection. The later the primary maternal infection occurs, the more likely the infection will be transmitted to the fetus. However, the earlier the fetus acquires the infection, the more severe the consequences. Early fetal *T gondii* infections can involve the brain, which may lead to permanent neurologic injury. Disseminated toxoplasma may cause fetal death. However, cases of stillbirth attributed to toxoplasmosis are generally sporadic, and in most developed countries the overall contribution to fetal death is undoubtedly small. The situation in developing countries may be different. For example, in Zimbabwe, serologic tests for toxoplasmosis were 4-fold greater in stillbirths than in controls. Whether toxoplasmosis was the etiologic factor is unknown.

**Q fever.** Q fever is a rickettsial infection caused by a gram-negative obligate intracellular bacterium, *Coxiella burnetti*. In humans this infection is generally acquired by inhalation of infected aerosols during contact with domestic animal meat products, although transmission has occurred by tick bite and ingestion of infected milk. Human infections have been described in nearly all countries. In nonpregnant adults, *C burnetti* causes pneumonia, meningoencephalitis, hepatitis, and endocarditis. Infections may be acute or persistent, with the latter mostly asymptomatic, except during pregnancy when the organisms may infect the placenta, leading to abortion, stillbirth, and preterm birth. In a recent review of the reported cases of acute Q fever during pregnancy which have occurred to date, the authors note that abnormal pregnancy outcomes were found in all cases of acute maternal infection, with fetal death occurring in two thirds and preterm birth in one third. Organisms were generally isolated both from the placenta and from fetal tissue. Most of the fetal deaths occurred in the second and early third trimester. The overall contributions of Q fever to stillbirths, and the actual geographic distribution of Q fever-associated stillbirths, is unknown. Rocky Mountain spotted fever is also a rickettsial disease with widespread distribution in the United States. There are no reports of stillbirth or even intrauterine infection associated with maternal infection.

**Viral diseases.** Although it is clear that viruses can cause stillbirths, the overall nature of this relationship is less than clear. Many viruses are difficult to culture, a positive viral serologic result does not prove causation, and DNA or RNA viral identification has only recently become widely available and is technically difficult. That said, the clearest relationship between any virus and stillbirth is with parvovirus.

Parvovirus (B19) causes a common childhood exanthem—erythema infectiosum—or fifth disease (slapped cheek disease) and aplastic anemia in children with sickle cell disease. It was first associated with fetal death in 1984. Subsequently, investigators have shown that parvovirus crosses the placenta and preferentially attacks erythropoietic tissue, causes severe fetal anemia, nonimmune hydrops, and fetal death. The virus also attacks fetal cardiac tissue and may cause fetal death as a result of cardiac damage. Most fetal deaths occur in the second trimester and are associated with hydrops, although some investigators believe that parvovirus is an important cause of nonhydropic third-trimester fetal death as well.

Previous infection elicits an antibody response that is protective against subsequent maternal and fetal infection. About half of all pregnant women in the United States have had a previous infection, have circulating antibodies, and are immune. Of the half who are not immune, with continued exposure about 25% will acquire the disease, and of these about 30% will pass the virus to their fetus. Of the infected fetuses, only about 10% will have hydrops or other manifestations of fetal infection. Most of these fetuses will not die. Therefore, when the mathematics are done, even with maternal parvovirus infection, the risk of stillbirth associated with maternal infection is quite low. There are a number of reported series in which few, if any, stillbirths appear to have been caused by parvovirus. On the other hand, in a series recently reported from Sweden, where polymerase chain reaction for viral DNA rather than serology and culture were used to define fetal parvovirus infection, 15% of all stillbirths were attributed to parvovirus. In another study in Sweden, 6 of 77 (8%) stillbirths were due to parvovirus.

Therefore, it is difficult to say with certainty the proportion of all stillbirths that may be attributable to this infection. Nevertheless, at present, it appears that the primary mechanism leading to fetal death involves the virus’ predilection for bone marrow, resulting in fetal anemia and hydrops. The infections that result in...
stillbirth are generally acquired before 20 gestational weeks, and death usually occurs in the mid trimester. Late stillbirths are rarely caused by parvovirus infection. Overall, in the United States it appears that fewer than 1% of all stillbirths result from parvovirus infection.

Each of the common viral childhood illnesses (chickenpox, rubella, measles, and mumps) have been implicated in stillbirths in association with a maternal infection. For example, chickenpox occasionally bypassed some children, who therefore did not develop immunity, and later had chickenpox as an adult during pregnancy. The results were often devastating. Pregnant women often had severe systemic illnesses and were at risk for losing their own lives as well as those of their fetuses as a result of the associated pneumonia. The varicella virus also occasionally traversed the placenta and attacked the fetus directly, occasionally damaging a vital organ, killing the fetus. Even before the advent of varicella immunization, these stillbirths occurred only sporadically. Because of widespread immunization, the incidence of chickenpox in pregnancy will decrease, and the associated stillbirths should decrease as well.

Rubella virus, the etiologic agent for German measles, was first associated with congenital cataracts by Gregg in 1941. Subsequently, a wide variety of anomalies have been documented, including major cardiac defects. Some of these, as well as infections of the fetal brain, may result in stillbirths later in pregnancy. Transmission of the virus to the fetus is most likely to occur with maternal disease during the first trimester, with the risk of fetal damage generally decreasing as the gestational age increases. Rubella also infects the placenta, enhancing the risk of stillbirth, and can apparently do so without fetal spread.

With the development of the rubella vaccine and its widespread adoption, congenital rubella infection has become extremely rare in developed countries and plays virtually no role in stillbirths in these locations. Its contribution to stillbirths in developing countries is unknown. Maternal infection with both mumps and rubella, or regular measles, have been implicated, although rarely, as a cause of stillbirth, and both viruses have been isolated from fetal tissues. Because of routine vaccination, reports from developed countries contain no recent reports of stillbirth in association with these viruses. However, in a 1988 report from Guinea-Bissau, stillbirth rates increased 4- to 9-fold if the mother was infected with measles during her pregnancy.

The enterovirus family includes enterovirus, echovirus, Coxsackie virus, and polio. Each can cross the placenta, and each can cause fetal death. For example, a case report described a woman who had Coxsackie virus A9 meningitis at 33 weeks’ gestation. Two weeks later she was delivered of a stillborn infant whose placenta showed parvillous fibrin deposition and villous necrosis with inflammatory cell infiltration. Coxsackie virus A9 was cultured from the placenta. In another case report, Coxsackie virus B3 was associated with calcific pancarditis and hydrops fetalis. Furthermore, in a recent study from Sweden, among 21 women with stillbirth, 52% were Coxsackie B virus positive, whereas among controls, only 22% were positive. In a study from Louisiana, three stillborn infants were documented to have intrauterine myocardial infections with Coxsackie B virus. Echoviruses and enteroviruses have also been cultured from stillborn autopsy material in which the cause of death appeared to be a fetal viral infection. However, some of the fetal deaths appear to be the result of maternal illness and dehydration. Before polio was eradicated from the United States, occasional stillbirths were thought to occur because of maternal viral infection. Most of these occurred as a result of severe maternal illness and respiratory failure, but in individual cases the virus appeared to have crossed the placenta and killed the fetus.

Cytomegalovirus (CMV), a member of the herpesvirus family, is the most common congenital viral infection. In the United States, about 1% of pregnant women acquire primary CMV during pregnancy. The highest rate of transmission to the fetus, and the most severe consequences, occur with primary maternal infection, probably because of lack of transferred immunity. In many women, the CMV infection is chronic. However, despite the presence of maternal antibodies, the fetus is at some risk. CMV affects 0.2% to 4.0% of newborn infants in the United States, and about 11% of these, or 1:1000 births, are severely affected and may have pneumonia and multiorgan failure. Central nervous system damage may also result in severe neurologic morbidity or death. Placental involvement is well documented. Most prospective studies do not mention stillbirths as an outcome associated with CMV infection, although case reports suggest an association. However, Griffiths and Baboonian in a prospective study of more than 10,000 women found an increase in fetal loss associated with early CMV infections. Whether CMV actually causes stillbirth and, if so, the mechanism by which it does so, is not clear.

The common maternal genital tract herpesvirus infection, which is caused by the herpes hominins virus type 2, has rarely, if ever, been implicated as a cause of stillbirth. The lack of association is likely explained by the fact that the virus rarely causes an intrauterine infection and neonatal infections are acquired during fetal passage through an infected birth canal. Although not seen clinically for more than a quarter century, Bernirschke and Robb note that, before its elimination, maternal smallpox infection frequently caused fatal damage to fetuses, who at the time of autopsy, had extensive necrotic lesions as well as destructive placental lesions. Because of the potential to use the smallpox virus as a biologic weapon, the return of this once-common cause of stillbirth is, of course, possible.
Finally, the human immunodeficiency virus (HIV) may cross the placenta and infect the fetus before delivery. Virus has been cultured from spontaneous abortion tissue as well. Although most studies show no relationship between maternal HIV infection and stillbirth, in the largest study, women who were HIV positive were statistically more likely to have a stillborn infant. That said, because women who are HIV positive tend to have other risk factors for stillbirth and because HIV generally causes little or no placental or fetal organ damage in utero, it is not likely that HIV is causal for stillbirths, other than in those cases where the mother has a severe systemic illness resulting from the HIV. To be complete, the lymphocytic choriomeningitis virus has also been implicated as a cause of stillbirth.  

**Bacterial infections.** A review of the literature on infection and stillbirth leads to the conclusion that there are a wide variety of bacteria that infect the placenta, membranes, or the fetus itself and that have been associated with stillbirth. For the following discussion, we will divide bacterial infections into those which likely reach the fetal compartment ascending from the vagina through the cervix and those that reach the fetal compartment hematogenously through the placenta.

**Ascending bacterial infections.** The types of organisms that ascend from the vagina and infect the uterus and the mechanism by which they cause fetal death have generally been similar over time and across geographic areas. However, the percent of all pregnancies affected by intrauterine bacterial infection differs across populations and by gestational age within populations. The organisms likely ascend from the vagina into the uterus during early pregnancy, but clearly some reside in the uterus before pregnancy. They enter the amniotic fluid either through intact choriodecidual membranes or after the membranes rupture and ultimately infect the fetus. The most common pathway of attack is by way of the fetal lung, probably associated with fetal breathing of contaminated amniotic fluid. This mechanism of infection would explain why the most common autopsy finding for many bacterial infection–related fetal deaths is pneumonitis.

Over the last 50 years, a number of authors have related amniotic fluid bacterial infection to fetal death. However, in recent years, amniotic fluid infection has been studied most frequently in relation to preterm birth. From this literature, it is now clear that women who have bacterial vaginosis, and even some women who do not, may have an ascending bacterial infection, usually before membrane rupture, causing a decidual and chorioamnion infection and inflammatory response. In about half the cases, this infection is limited to the chorioamnion, but in many others the bacteria appear to traverse the membranes and infect the amniotic fluid. Only occasionally do these organisms appear to infect the fetus. The organisms involved are most frequently *Ureaplasma* and *Mycoplasma hominis*, but a large variety of other bacteria including *Bacteroides*, *Gardnerella*, *Mobiluncus*, various enterococci, and many others can cause this infection. For the most part, the organisms are of low virulence and apparently can reside in the uterus for weeks or months before precipitating preterm labor. Even with the onset of labor, most women do not have classic signs of infection such as fever, chills, or an elevated white blood cell count. Instead, the symptoms of this infection, for the most part, seem to be contractions, and eventually, ruptured membranes. Occasionally, more virulent organisms follow this same pathway and infect the uterine cavity before rupture of membranes. Clearly, organisms such as group B *Streptococcus*, *E coli*, *Klebsiella*, and even staphlococci have crossed intact fetal membranes and have caused amniotic fluid infection. When infection occurs with these types of organisms, the inflammatory response appears to occur much more rapidly and is more severe, with labor ensuing within hours to days.

Whether the amniotic fluid infection occurs in the presence of intact membranes or follows membrane rupture, the organisms are then aspirated, enter the fetal lung, and may cause severe infection. Whether the fetus is stillborn with congenital pneumonitis or is born alive with pneumonia may depend on factors such as the length of time between infection and delivery. Note that a preterm fetal infection generally elicits a fetal inflammatory response and ultimately initiates preterm labor. They suggest that if the fetus cannot initiate an adequate inflammatory response leading to labor or membrane rupture the outcome is likely to be a stillbirth.

Amniotic fluid infection has been described in many geographic locations. In most areas, it is a common cause of preterm birth and a more or less common cause of stillbirth. What is also clear is that the frequency of this infection varies by gestational age. Births before 28 weeks appear to be strongly associated with amniotic fluid infection, whereas late preterm births and births at term are much less likely to have an associated amniotic fluid infection. Therefore, the apparent prevalence of this condition in a population will depend on whether all stillbirths from 20 weeks onward are evaluated or whether the geographic area solely evaluates preterm births at 28 weeks or later or, in fact, only evaluates term stillbirths.

The evidence that this type of amniotic fluid infection either is associated with or causal for stillbirth comes from several different types of studies. The first type includes comparing the placental histologic features in fetal deaths with placentas from various types of control groups. In virtually all these studies, the frequency of histologic chorioamnionitis in the stillbirth group is several times greater than in a control group. Furthermore, the more stringent is the required histologic evidence for infection, the more likely this finding will be present in
the stillbirth group compared with the control group. Therefore, the presence of funisitis, or the presence of chorionic plate inflammation, is often far greater in the stillbirth group than in appropriate controls. More impressive is the finding of organisms in internal organs at the time of autopsy, in conjunction with histologic evidence of inflammation. For example, there are a number of stillbirth autopsy studies that have shown that organisms such as group B Streptococcus, E coli, and Klebsiella as well as enterococci are likely to be cultured from fetal heart blood, liver, lung, or brain.\(^{104,106,109,116}\)

In studies from a wide variety of locations, including Sweden, Lithuania, the United States, and a number of sites in Africa, these findings are consistent. From Lithuania, for example, fetal bacteremia was found in 36% of the stillbirths but in none of the controls, with more than half the cases caused by \(E\) coli. The placenta frequently showed histologic chorioamnionitis and vasculitis.\(^{109}\)

Organisms in internal organs were much more common in early gestational age stillbirths than later gestational age stillbirths. Bergstrom et al, in a series of studies from Mozambique and Zimbabwe, have carefully studied this phenomenon in these two African populations.\(^{60,103,104,107,108}\) For example, they have found \(E\) coli in 25% of samples of heart blood drawn from stillborn infants in Zimbabwe and have consistently found organisms in internal organs at the time of autopsy.\(^{60}\) They note that the organ most commonly affected is the fetal lung. In another study from Ethiopia, Tafari et al\(^{101}\) noted that, although \(E\) coli and other bacteria were the organisms most often responsible for fetal death, in 23 of 290 (8%) perinatal deaths (mostly late stillbirths) the only organisms identified as responsible for the congenital pneumonia and fetal death were mycoplasma T strains. These infections apparently occurred through intact membranes.

Perhaps the most elegant series of studies was done by Naeye et al\(^{17}\) who studied stillbirths in Ethiopia but also had the luxury to compare these results to findings from the US Collaborative Perinatal Study. In 1977, they noted that the mechanism of infection (ie, ascending from the vagina to the intrauterine cavity) appeared similar in both geographic locations. However, they noted that the frequency of stillbirth associated with infection was several times greater in Ethiopia than in the United States. They went on to observe that the rate of infection in early pregnancy tended to be similar in the United States and in Africa. However, although the rate of infection-related stillbirth declined as the gestational age increased in the United States, it persisted at relatively high rates throughout the length of pregnancy in Ethiopia. The authors speculated that the difference had to do both with the burden of exposure to infectious organisms, which appears to be much greater in Africa, as well as a decreased immune response, which was believed to be related to the malnutrition so prevalent in African populations. On the basis of histologic observations from Ethiopia, Naeye et al\(^{17}\) concluded that approximately 15% of all Ethiopian pregnancies were associated with an amniotic fluid infection.

In developed countries, the bacterial amniotic fluid infection rate appears to be lower than in developing countries but still plays an important role in stillbirth. For example, in a recent review of all the stillbirths that occurred in Stockholm, Sweden, in 1998 and 1999, infections were estimated to have caused 24% of all stillbirths.\(^{120}\) In a study from Lund, Sweden, 21% of all stillbirths were caused by infection, with the majority being bacterial in origin. The authors note that \(E\) coli, group B streptococci, and enterococci were the major organisms found in internal organs at autopsy. Bergstrom\(^{121}\) noted that in the US Collaborative Perinatal Study amniotic fluid infection was the most important causative factor in perinatal deaths.

Of all the bacterial infections associated with stillbirth, special emphasis should be given to group B Streptococcus.\(^{110-115}\) In the middle decades of the 20th century, many reports from developed countries associated stillbirth with an intrauterine infection with this organism. Many of these infections apparently occurred in the presence of intact membranes,\(^{111}\) but the most common scenario described an intrauterine infection after spontaneous membrane rupture. In one study, 11 of 113 (9.3%) consecutive stillborn infants had group B streptococci cultured from internal tissues at autopsy.\(^{113}\) In another, at autopsy, 45% of midtrimester stillbirths were associated with a group B streptococcal infection.\(^{114}\) Stillbirths associated with group B streptococcal infection virtually always had a congenital pneumonia.\(^{114}\) Overbach et al\(^{122}\) noted that, as opposed to many other intrauterine infections, fetal infection with group B Streptococcus might not involve inflammation of the fetal membranes. They suggested that, when the organisms enter the uterus after membrane rupture, rapid bacterial replication occurs in the amniotic fluid and in the fetus with little infection in the membranes themselves. Christensen et al\(^{115}\) noted that fetal mortality associated with group B streptococcal infection often occurred so rapidly that there was often minimal fetal inflammatory response. Although stillbirth cases associated with group B streptococci appear to have decreased substantially in the United States in recent years—perhaps associated with the introduction of various types of screening and treatment programs—in Sweden, which does not routinely screen and treat, group B Streptococcus is the most common bacterial infection associated with stillbirth.\(^{129}\) In developing countries, group B Streptococcus has consistently been found to be less prevalent in pregnant women and neonates. In those countries, it is likely not to be as important a cause of stillbirths as \(E\) coli and other gram-negative bacteria.
Two other organisms should be mentioned, Chlamydia trachomatis and Neisseria gonorrhoeae. Although clearly among the most important organisms causing sexually transmitted infection, neither appears to be an important cause of stillbirth. That said, in case reports, both organisms have been found in internal organs at the time of a stillbirth autopsy—but only rarely. The reason for their lack of involvement in stillbirths may be related to the fact that, as opposed to many other bacteria such as U urealyticum or even group B Streptococcus, during pregnancy neither bacteria appears to routinely ascend into the uterus, and neither is commonly found in the uterus associated with preterm labor. Galask et al suggest that, at least for N gonorrhoeae, the reason for the failure to ascend into the uterus during pregnancy is due to its inability to attach to the fetal membranes. In any case, if these organisms are not routinely found in the pregnant uterus, their ability to cause stillbirth is likely quite limited.

Hematogenously acquired bacterial infections. Bacteria can also reach the fetus through the placenta. When that occurs, in many instances the placenta has evidence of infection, including an inflammatory white blood cell response, microabscesses, and areas of infarction. The organisms generally appear to enter the fetus through the umbilical vein, and for that reason the liver is the organ most often infected, although other organs such as the brain are often involved as well. Listeria monocytogenes is an excellent example of a hematogenously transmitted organism that has caused fetal death. This infection is acquired by the mother, usually through her gastrointestinal tract by eating contaminated food. The organisms are most often transmitted hematogenously to the placenta and may cause villous necrosis and microabscesses. In some cases, the organisms are transmitted to the fetus and the fetal deaths are attributed both to placental dysfunction, often associated with growth restriction, and the direct infection of the fetus.

On rare occasions, bacterial infection of the fetal liver and stillbirth has been reported in association with maternal tularemia, anthrax, typhoid fever, and brucellosis. Other organisms that have been implicated in fetal death and likely were transmitted to the fetus transplacentally include a plant bacteria, Agrobacterium radiobacter, Haemophilus influenzae, Pseudomonas pyocyanea, and even Candida albicans. Clostridial infections have also been implicated in fetal death.

Referring to the potential mechanisms of death associated with infection-caused stillbirth, to this point, we have predominantly considered those amniotic fluid infections in which the organisms attack the fetus directly causing pneumonitis and sepsis. However, it is also apparent that many of the earliest stillbirths occur without the organisms actually reaching the fetus. Instead, bacterial infections appear to cause stillbirth by precipitating preterm labor, and perhaps intrauterine bleeding, with the fetus dying in relationship to one of those conditions. Placental damage, including thrombosis, resulting from these infections also may cause decreased oxygenation, resulting in stillbirth by that mechanism.

Overall, by a number of mechanisms, it appears that in developed countries, between 1 and 2 pregnancies in 1000 end up with a stillbirth caused by a bacterial infection. With overall stillbirth rates from 20 weeks through term ranging from 6 to 8 per 1000 births in many developed countries, this suggests that somewhere between 1 and 2 of the 6 to 8 per 1000 stillbirths occur in relation to a bacterial intrauterine infection. In developing countries, where the stillbirth rates may be 10 times those seen in developed countries, it appears that a much larger proportion of the stillbirths is related to bacterial intrauterine infection.

Prevention of infection-related stillbirth

Because of the very low incidence of infection-related stillbirths in many developed countries, reducing this component still further may be quite difficult. Even if vaccines were developed for some of the viral causes of stillbirth (parvovirus, Coxsackie A and B), this would have only a small impact on the stillbirth rates. Stillbirths with toxoplasmosis occur so rarely that educational attention to hand washing, cat litter boxes, etc, will not have a discernible impact. Greater attention to preventing and treating Lyme disease might reduce the few stillbirths associated with this condition. However, the largest potential benefit appears to be related to stillbirths associated with bacterial intra-amniotic infections. In a number of geographic areas, health care providers do not screen for or treat group B Streptococcus, and certainly stillbirths caused by this organism occur both before and after membrane rupture. The high percentage of group B streptococcal-related stillbirths in Sweden, a country that does not routinely screen for this organism, suggests room for improvement. On the other hand, although not a consistent observation, antibiotic prophylaxis against group B streptococci may be associated with an increase in fetal gram-negative and especially E coli infections. Therefore, it is unknown whether group B streptococcal screening and treatment programs will actually reduce the number of stillbirths associated with this organism or even whether they reduce the overall infection-related stillbirth rate because they may substitute stillbirths associated with one organism for another. Also, although there have not been large numbers of stillbirths associated with ascending bacterial infection after premature rupture of the membranes (PROM), the current recommended antibiotic treatment strategies certainly reduce chorioamnionitis and will likely reduce stillbirth as well. It is unknown whether treatment of bacterial
vaginosis will reduce stillbirth rates. However, continued attention to screening and treatment of the sexually transmitted infections, including syphilis, chlamydia, and gonorrhea should keep the stillbirths associated with these infections to a minimum.

In many developing countries, the infectious disease burden during pregnancy is extremely high, and it appears that in many countries the stillbirth rate is high as a result of these infections. Therefore, in some countries, effective programs to screen for and treat syphilis and the other sexually transmitted infections should have a major impact on the number of stillbirths. Reducing maternal malaria infection in newly endemic areas or in newly infected pregnant women in endemic areas should also reduce the stillbirth rate. In developing countries, it is also likely that reduction in amniotic fluid infections, if achievable, will also have a substantial impact on stillbirth rates. Potential strategies (which should be tested in appropriate randomized trials) for use in these countries include nutritional supplementation with vitamin/mineral preparations, calories, or both, and a reduction in genital tract bacterial exposure by use of antibiotics or vaginal/newborn chlorhexidine washes, and effective management of both preterm and term PROM. Achieving high antiviral vaccination rates (rubella, varicella, polio, etc) should reduce the stillbirths associated with these maternal infections. Most important, for developing countries, it is crucial to monitor the infection-related stillbirths, so that the number of stillbirths associated with specific infections will be known and effective strategies to reduce their occurrence can be initiated.

**Comment**

In summary, in developed countries, the most common intrauterine infection causing stillbirths appears to be caused by bacteria ascending from the vagina. In developing countries, most infection-related stillbirths appear to be caused by *T. pallidum*, malaria, and intrauterine infection with common vaginal organisms.

However, overall, the fetus is relatively well protected from infections while in utero and, at least recently in developed countries, rarely dies in utero as a result of infections. This conclusion is tempered slightly because so much of the work on perinatal infections has been done by researchers who focused more on neonatal death than on stillbirth. For obstetricians, the best proof of an infectious etiology for a stillbirth is a carefully performed autopsy with appropriate serologic studies, cultures, and DNA specimens taken for the organisms discussed in this report. However, even if an autopsy is not performed, a histologic study of the placenta, membranes, and umbilical cord, with appropriate bacterial, viral, and protozoan serologic studies, culture, and DNA isolation techniques, will often provide evidence for an infectious etiology.

**REFERENCES**