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Infectious Causes of Stillbirth: A Clinical Perspective

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Abstract

Untreated infection may cause stillbirth by several mechanisms, including direct fetal infection, placental damage, and severe maternal illness. Many bacteria, viruses, and protozoa have been associated with stillbirth. In developed countries, up to 24% of stillbirths have been attributed to infection, although with increased availability of sophisticated diagnostics and rigorous screening, it appears likely that higher numbers may actually be associated with infection. In developed countries, ascending bacterial infection is usually the most common infectious cause of stillbirth, with a number of viral infections also an important factor. Screening, prevention and treatment of maternal infections are important to reduce stillbirth risk.

Keywords

Stillbirth; infection; chorioamnionitis

One of the major adverse pregnancy outcomes is stillbirth, with more than 3.2 million stillbirths occurring each year worldwide. (1) In the U.S., about 26,000 stillbirths occur each year, about the same as the number of neonatal deaths. Almost 80% of stillbirths are preterm and about half of all stillbirths occur prior to 28 weeks. In developed countries such as the U.S., up to 24% of all stillbirths have been attributed to maternal or fetal infections. (2–6) Furthermore, a significant number of stillbirths are multi-factorial and thus infection may contribute to many more.

The relationships between maternal infection and stillbirth may be unclear for several reasons. First, infection is often not apparent from the case history or physical examination of the mother or fetus. Routine histologic evaluations of the placenta and fetal autopsy may miss organisms that contribute to fetal death. Performing external skin or ear cultures to document an infection has not proven helpful in determining cause of stillbirth. Neither positive serologic tests nor organisms cultured from the placenta or even the fetus prove causality. Even when evidence of infection is present, identifying precisely why a specific stillbirth occurred is difficult. In addition, a fetal autopsy and histologic study of the placenta may have findings suggestive of other etiologies as well as infection. In these cases, whether the death should be attributed to infection is often uncertain. Finally, infection may initiate

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the events leading to stillbirth, and its contribution to the fetal death may not be appreciated (e.g. parvovirus infection causing hydrops or early rubella infections causing congenital anomalies). An important related factor is that infection is more often causally associated with early (20–28 weeks) compared to late stillbirths (after 28 weeks). Because of this relationship, studies that only evaluated later fetal deaths, have often missed the large contribution of infection to early fetal deaths.

Mechanisms

Stillbirth may result from maternal or fetal infection through a variety of mechanisms, including direct infection, placental damage, and severe maternal illness. First, the fetus may be directly infected via the placenta or membranes, with the organisms damaging a vital organ such as the lung or heart. Second, the placenta may be directly infected without fetal involvement, resulting in reduced blood flow to the fetus. When early infection occurs, the fetus may develop a congenital anomaly with a subsequent fetal death due to the anomaly. Third, maternal infection may lead to a severe maternal illness. Due to high maternal fever, poor oxygenation or systemic reaction to the illness, the fetus may die without transmission of organisms to the placenta or fetus. Finally, maternal infection may precipitate preterm labor, with the fetus unable to tolerate delivery resulting in stillbirth. Stillbirths have been associated with almost every type of infection, including those caused by bacteria, viruses, and many parasites. Nevertheless, of the thousands of infectious agents in the environment, relatively few have been proven causal for stillbirth. Moreover, as with many purported causes of stillbirth, a key question is why some women with common infections suffer stillbirth, while other women accomplish a normal pregnancy outcome.

Infections Associated with Stillbirth

A large number and variety of bacterial, viral, protozoal and fungal infections have been associated with stillbirth. We have reviewed these in detail elsewhere, but will highlight some infections of interest here. (3,4) (Table 1)

BACTERIAL INFECTIONS

More than 130 bacterial species cause intrauterine infection and at least a third of these have good evidence for being causal for stillbirth. These infections may be divided into those which reach the fetal compartment by 1) ascending from the vagina through the cervix or 2) reaching the uterus hematogenously through the placenta. (Figure 1)

Ascending bacterial infections

With these infections, the organisms generally ascend from the vagina into the uterus during pregnancy, but many have low virulence and may reside in the uterus prior to pregnancy. The organisms most often infecting the uterus are *U urealyticum* and *Mycoplasma hominus*, but a large variety of other bacteria including group B *Streptococcus (GBS), E coli*, Bacteroides spp, *Gardnerella, Mobiluncus spp*, and various enterococci can cause this infection. These organisms may enter the amniotic fluid either through intact choriodecidual membranes or after the membranes rupture and ultimately may infect the fetus. The most common pathway to fetal infection is via the fetal lung, associated with fetal breathing of contaminated amniotic fluid. This explains why the most common autopsy finding for many bacterial infection–related stillbirths is pneumonitis. Depending on the length of time between infection and delivery, the fetus may be stillborn with congenital pneumonitis or born alive with pneumonia. Romero et al (7) note that a preterm fetal infection generally elicits a fetal inflammatory response, initiating preterm labor. If the fetus cannot initiate an

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adequate inflammatory response leading to labor or membrane rupture, stillbirth will likely result.

The frequency of amniotic fluid infection, a common cause of stillbirth, varies by gestational age. Both live births and stillbirths before 28 weeks are strongly associated with amniotic fluid infection, whereas late preterm and term births are much less likely to be associated with this infection. In most studies more than half of all stillbirths at less than 28 weeks have an associated histologic chorioamnionitis. For example, Lahra *et al*. in Australia found a very strong relationship between gestational age and the presence of histologic chorioamnionitis. (8) (Figure 2) In a study from Sweden, 24% of all stillbirths were attributed to infection with *E coli*, group B streptococci, and enterococci, the predominant organisms found in internal organs at autopsy. Naeye (9) noted that in the U.S. Collaborative Perinatal Study, amniotic fluid infection was the most important cause of perinatal deaths.

Transplacental bacterial infections

Bacteria, as well as most other infectious agents, also reach the fetus through the placenta. When that occurs, the placenta will often have evidence of infection such as a white blood cell response, micro-abscesses, and infarction. The organisms generally enter the fetus through the umbilical vein; for that reason the liver is the organ most often infected. *Listeria monocytogenes* is an example of a hematogenously transmitted organism that causes fetal death. Infection is acquired by the mother, usually by eating contaminated food with organisms transmitted hematogenously to the placenta. 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 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, and brucellosis, a plant bacteria, *Agrobacterium radiobacter*, *Haemophilus influenzae*, *Pseudomonas pyocyanea, and* Clostridial infections among others.

A number of spirochetal infections have also been determined to be causally associated with stillbirth by transplacental transmission. *Treponema pallidum*, the spirochete responsible for syphilis, can cross the placenta and infect the fetus at >14 weeks' gestation, with risk of fetal infection increasing with gestational age. If the fetus is infected, about 45% will die *in utero*, with another 30–40% born alive but with signs of congenital syphilis. (10) Other spirochetal diseases causal for stillbirth include Leptospirosis and Lyme disease. While stillbirths have been attributed to Lyme disease in case reports - with most deaths occurring in the mid-trimester - except in highly endemic areas, the number of stillbirths caused by Lyme disease appears small.

VIRAL INFECTIONS

A number of viruses have also been causally associated with stillbirth. Parvovirus B19, one of the best studied viruses, crosses the placenta and preferentially attacks erythropoietic tissue, causing fetal anemia, non-immune hydrops, and fetal death. (11) In the US, <1% of stillbirths are associated with parvovirus infection but in Sweden and Germany about 10% of stillbirths may occur secondary to a parvovirus infection. Enteroviruses, including echovirus, Coxsackie virus, and polio, can all cross the placenta and cause fetal death. (12) In one study of unexplained perinatal deaths, Coxsackie virus was present in 48% of cases, while another study from Sweden, found Coxsackie virus among 52% of stillbirths compared to only 22% of controls. (13,14) Hepatitis E virus infection has also been associated with stillbirth. Additionally, many childhood illnesses, including chickenpox, measles, German measles and mumps had been associated with stillbirth prior to widespread vaccination programs. (15)

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Influenza has been associated with excess deaths among pregnant women during pandemics. (16) The influenza-associated mortality rate of pregnant women who develop pneumonia in the third trimester approaches 60% and in these cases the fetus often dies as well. There are increased fetal, medical, and obstetrical complications from seasonal influenza with reporting of fetal death clusters in association with influenza A. In the recent epidemic, SARS was demonstrated to be associated with placental and fetal pathology, though its association with pregnancy outcome needs further research. (17) Influenza generally has not been causally associated with stillbirth, although the 2009 epidemic of H1N1 has had at least one stillbirth associated with it. (18) Most studies also show little evidence indicating a causal relationship between maternal HIV infection and stillbirth, although in several studies, HIV-infected women were statistically more likely to have a stillborn infant. (19)

PROTOZOAL and FUNGAL INFECTIONS

A number of protozoal infections have been associated with stillbirth, including malaria, African sleeping sickness (carried by the tsetse fly) and Chagas disease, an infection commonly seen in central and South America, but most of these infections are rarely seen in the US. Toxoplasmosis has occasionally been documented as a cause of stillbirth as has Q fever. Fungi rarely cause stillbirth, but there are documented cases of several *Candida spp* causing stillbirth.

VECTOR and ANIMAL - BORNE INFECTIONS

In a review of infections in pregnancy, mostly targeting developing countries, we noted numerous vector-borne and animal-borne infections that have been associated with stillbirth. (4) (Table 2) For example, ljungan virus, a picornavirus of bank voles, was originally isolated in Sweden and has since been reported as a cause of human stillbirth in Denmark and the US. (20)

Determining infection as causal for stillbirth

Since the 1950s, more than 30 different classification systems have been developed to assign cause of stillbirth. Generally, available information about the maternal and/or fetal conditions is applied to the classification system's criteria to assign a primary or underlying cause of stillbirth. Among the systems available are the Wigglesworth, Aberdeen, and the Relevant Conditions at Death (ReCoDe). (21–23) The Wigglesworth system uses a pathophysiological approach, combined with stratification by birthweight classes, to create functional groups. The Aberdeen classification, originally developed in 1954, ascribes the death to predisposing obstetric events or to the underlying cause. (21,22) A more recent system, ReCoDe, attempts to identify the relevant conditions present at the time of death *in utero*. (23)

NICHD recently held a workshop, "Stillbirth Classification—Developing an International Consensus for Research", to examine the existing systems and to develop a general methodology for evaluating conditions and their causal association with stillbirth. (24) This approach, which evaluates infectious as well as other causes, is based on the following principles: 1) there is epidemiologic data to support the association of a specific infection with the stillbirth, 2) there is biologic plausibility that the specific infection can cause stillbirth, 3) the infection is rarely seen in live births (or significantly associated with neonatal deaths), 4) a dose response relationship exists, 5) the infection is associated with fetal compromise and finally 6) the stillbirth would not have occurred without that infection. Most important, in reviewing gaps of existing systems, it became apparent that rigorous attention was needed to define the association between the infectious condition and the stillbirth. When considering infection as a cause of stillbirth, do we consider any existing

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maternal infection or only those infections with certain characteristics? Using the latter approach, a group in the U.S., the Stillbirth Collaborative Research Network (SCRN), has defined the criteria necessary for an infection to be considered a cause of stillbirth and also the degree of certainty of that relationship, e.g., as probably causal, possibly causal, or present without sufficient evidence to implicate causation. (25) Thus, based on this work, we believe that with an appropriate evaluation and sufficient data, the degree to which an infection may be related to the stillbirth may often be established as follows:

1. For a stillbirth to be considered caused by a maternal infection without fetal or placental involvement, we believe that the maternal infection should be severe, generally requiring hospitalization and often defined by high maternal fever, respiratory complications and/or surgery. In addition, the stillbirth should occur in close temporal proximity to the severe maternal infection. Severe pyelonephritis, pneumonia, influenza, and a ruptured appendix are some examples.
2. Direct fetal infection as a cause of stillbirth should be demonstrated by histologic evidence of fetal organ damage plus culture, histologic or PCR evidence of the presence of a specific organism, especially in an internal fetal organ.
3. Placental infection as a cause of stillbirth should show extensive placental involvement or damage – usually in the interstitial villous area – with demonstrated presence of organisms known to cause fetal death in this manner. Placental malarial infection is the best example.
4. Infections early in pregnancy leading to congenital anomalies or other fetal conditions later associated with stillbirth are also considered an infectious cause of stillbirth. To make this diagnosis, demonstration of maternal infection at an appropriate time in pregnancy with a specific organism known to cause the fetal condition is required, as is confirmation that the fetus has that condition. First trimester maternal rubella infection is the prime example of this type of infection; parvovirus infection with fetal hydrops is another example.
5. A number of stillbirths occur with the initiation of labor at gestational ages deemed by the provider too early (often <26 weeks) to intervene by cesarean section. The cause of the preterm labor frequently appears to be an infection of the membranes often associated with histologic chorioamnionitis. We believe these cases should be classified as an infectious cause of stillbirth. Attributing stillbirth to this infectious pathway requires histologic chorioamnionitis plus an intrapartum death at less than 26 weeks.

As with many other conditions associated with stillbirth, it is often uncertain whether a finding related to infection should be considered causal for the stillbirth. For example, if the mother has a positive antibody test for syphilis and the fetus dies, but there is no histologic placental or autopsy evidence of lesions generally associated with syphilis, should syphilis be considered the cause of death? Similarly, if histologic chorioamnionitis is present in a fetal death at >26 weeks, and there are no other findings suggestive of an infectious etiology, should the histologic chorioamnionitis be considered the cause of death? To deal with such cases, we believe a classification system that incorporates the degree of certainty about the association between stillbirth and infection is very helpful. A stillbirth with fetal hydrops and severe anemia with a demonstrated maternal parvovirus infection was **probably** caused by that parvovirus infection. It is less certain that a stillbirth with only histologic chorioamnionitis was actually caused by that condition. Therefore, we believe that in a classification system that includes infection as a potential cause of death, a measure of the certainty of the association should be presented. If signs of infection are present but do not

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meet carefully defined criteria, those infections should simply be noted as present, but not described as the cause of death.

Evaluation

Once a stillbirth occurs, the question often arises about which tests to review or order to confirm or rule out an infectious cause of death. Various authors and the American College of Obstetricians and Gynecologists (ACOG) have evaluated the utility of available diagnostic tests. (26–28) From the routine prenatal laboratory tests, the results for syphilis, HIV, hepatitis B virus, rubella, chlamydia and gonorrhea should be reviewed. In cases of stillbirth, a repeat evaluation for syphilis is usually recommended. TORCH titers (Toxoplasmosis, Rubella, CMV, Herpes and "other") are also often recommended – but with little evidence for their use. Although traditionally advised in the evaluation of stillbirth in the U.S., these titers are rarely clinically useful. (26) Maternal serology for parvovirus may be informative in select cases. Most useful is a careful placental histological examination and autopsy with specific bacterial cultures and specimens for viral culture and PCR drawn and evaluated based on the pregnancy history and findings at autopsy. Because of contamination following membrane rupture or vaginal contamination during delivery, routine bacterial culture of the placenta is usually not useful. Culture of fetal heart blood or fluid from uncontaminated fetal sites during autopsy, however, occasionally provides surprising and useful information to determine an infectious etiology.

Comment: Reducing infection-related stillbirth

The stillbirth ratio in the U.S. is approximately 5–6 per 1000 births. With infections accounting for 10 to 24% of all stillbirths, this means that about in 1 in 1000 births in the U.S. will be a stillbirth caused by infection. With the rarity of this condition, the many varieties of bacteria, viruses and protozoa that may cause an infection-related stillbirth, and the different strategies necessary to prevent these infections, it is unlikely that further substantial reductions in U.S. infection-related stillbirths will be achieved in the foreseeable future. That said, a number of strategies implemented fully should reduce the risk of stillbirth associated with infection. Prenatal screening for infections such as syphilis is important because women identified early and appropriately treated have a stillbirth risk not much higher than the general population. The U.S. Public Health Task Force recently recommended routine screening of all pregnant women for syphilis to allow for prompt treatment to reduce stillbirths associated with this infection. (28) Further, in high incidence areas repeat testing in the third trimester may help to prevent stillbirths later in pregnancy. In addition, screening and treatment of other sexually transmitted infections, including chlamydia and gonorrhea should minimize stillbirths associated with these infections. Screening for GBS and treatment with antibiotics in labor may reduce the stillbirths associated with that infection. Some stillbirths have been associated with ascending bacterial infection after PROM. The current recommended antibiotic treatment strategies certainly reduce chorioamnionitis and improve several other newborn outcomes, and may reduce stillbirth as well. Although many of the viral infections related to stillbirth are not preventable by vaccines, continued high rates of routine immunizations for childhood illness (e.g., measles, mumps, rubella, varicella) should prevent stillbirth associated with those infections. Timely immunization of all pregnant women against influenza as recommended by ACOG should eliminate the stillbirths associated with that infection. (29) Reducing exposure to cat litter boxes and to soft cheeses should reduce the few stillbirths associated with toxoplasmosis and Listeriosis. From a research perspective – since ascending bacterial infection prior to membrane rupture seems to be the most important infectious cause of stillbirths, developing a better understanding of this infection as well as methods to reduce its occurrence is crucial to reducing the infection related stillbirths in the U.S.

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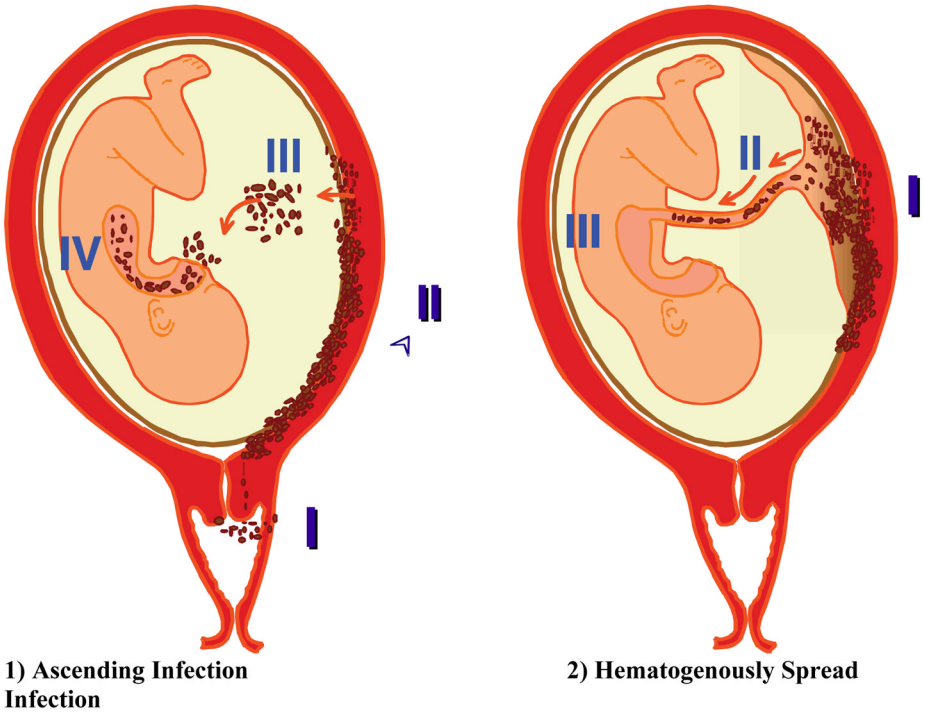

FIGURE 1.
Pathways to placental and fetal infection

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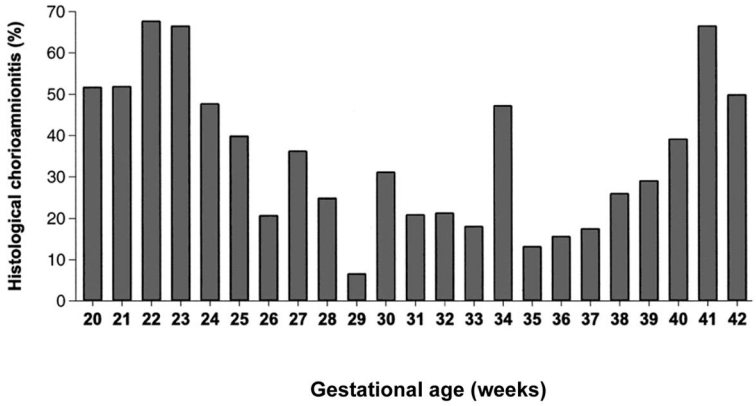

FIGURE 2.

Histologic chorioamnionitis in stillborn babies by gestational age (n=428)
Adapted from: Lahra MM, Gordon A, Jeffery HE. Chorioamnionitis and fetal response in stillbirth. Am J Obstet Gynecol 2007;196(3):229.e1–4.

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Table 1

Maternal infections and stillbirths

Organism	Maternal Disease	Comment
Bacteria **Ascending Bacterial Infections**		
Ureaplasma urealyticum	Generally asymptomatic	Confirmed as a cause of stillbirth
Mycoplasma hominus	Generally asymptomatic	Confirmed as a cause of stillbirth
E coli	Generally asymptomatic	Confirmed as a cause of stillbirth
group B *Streptococcus*	Generally asymptomatic	Confirmed as common cause of stillbirth
Klebsiella	Generally asymptomatic	Confirmed as a common cause of stillbirth
Enterococcus	Generally asymptomatic	Confirmed as a cause of stillbirth
Bacteroidaceae	Generally asymptomatic	Confirmed as a cause of stillbirth
Neisseria gonorrhoeae	Pelvic infection	Suggested as cause of stillbirth by case reports
Chlamydia trachomatis	Pelvic infection	Suggested as cause of stillbirth by case reports
Transplacental Bacterial Infections		
Treponema pallidum	Syphilis	Major cause of stillbirth when maternal prevalence is high
Borrelia burgdorferi	Lyme disease	Tick-borne infection and a confirmed but not common cause of stillbirth
Borrelia recurrentis	Relapsing fever	Tick-borne infection common in the western US and a confirmed but rare cause of stillbirth
Borrelia duttonii	Relapsing Fever	Tick-borne infection common in Sub-Saharan Africa and probably an important cause of stillbirth
Leptospira interrogans	Leptospirosis	Confirmed as cause of stillbirth but not common
Listeria monocytogenes	Listerosis	Confirmed as a cause of stillbirth; generally transmitted transplacentally
Other bacterial infections usually transmitted transplacentally include: Tularemia, Tuberculus Brucellosis, Clostridia, Typhoid, Anthrax, Streptococcus pseudoporcinus, Agrobacterium radiobacter, Pseudomonas, etc		Each organism has been implicated as causal for stillbirth by case reports
Viruses		
Parvovirus (B19)	Erythema infectiosum	Confirmed as cause of stillbirth and likely is the most common viral etiologic agent
Coxsackie A and B	Various presentations	Confirmed as causes of stillbirth and may be an important contributor to overall stillbirth rate
Echovirus	Various presentations	Confirmed as cause of stillbirth but of unknown importance
Enterovirus	Various presentations	Confirmed as cause of stillbirth but of unknown importance
Hepatitis E Virus	Fulminant hepatic failure	Probable cause of stillbirth especially in geographic areas with epidemic outbreaks
Polio virus	Polio	Historically likely cause of stillbirth but since routine vaccination is rarely seen in developed countries

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Organism	Maternal Disease	Comment
Varicella zoster	Chickenpox	Confirmed as a rare cause of stillbirth but with routine vaccination almost never seen
Rubella	German measles	Confirmed as a cause of stillbirth but rarely reported as a cause of stillbirth in developed countries
Mumps	Parotitis	Possibly a cause of stillbirth historically but rarely reported as a cause of stillbirth in developed countries
Rubeola	Measles	A probable cause of stillbirth historically but rarely reported as a cause of stillbirth in developed countries
Cytomegalovirus	Generally asymptomatic in adults	Reported as a cause of stillbirth in case reports but overall contribution is unknown
Variola	Smallpox	Historically a cause of stillbirth but with vaccination no longer seen
Ljungan virus	Diabetes, neurological disease, myocarditis and deaths	Carried by wild rodents, it is associated with several cases of stillbirth in a single report
Dengue virus	Dengue fever	Carried by mosquitoes and confirmed as a cause of stillbirth
Lymphocytic choriomeningitis virus	Lymphocytic choriomeningitis	A possible cause of stillbirth but of unknown importance
Human immunodeficiency virus	Acquired immunodeficiency syndrome	Associated with stillbirth but not likely causative
Protozoa		
Trypanosoma brucei	Trypanosomiasis	Carried by tsetse fly; a likely cause of stillbirth in southern Africa, but overall contribution unknown
Trypanosoma cruzi	Chagas disease	Carried by the Triatomine (kissing bug) and a confirmed cause of stillbirth in South America but overall contribution unknown
Plasmodium falciparum	Malaria	Carried by mosquitoes and likely an important cause of stillbirth in newly endemic areas or in newly infected women
Plasmodium vivax	Malaria	Carried by mosquitoes and a possible cause of stillbirth but likely less important than with *Plasmodium falciparum*
Toxoplasmosis gondii	Toxoplasmosis	Confirmed as a rare cause of stillbirth
Coxiella burnetti	Q fever	Confirmed as cause of stillbirth but of unknown importance
Fungi		
Candida albicans	Thrush, vaginitis	Confirmed as cause of stillbirth by case reports
Candida glabrata	Vaginitis	Confirmed as cause of stillbirth in IVF pregnancies by case reports

Adapted from: Goldenberg RL, Thompson C. The infectious origins of stillbirth. Am J Obstet Gynecol 2003;189(3):861–73.

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Table 2

Vector-Borne and Animal Derived Maternal Infections Associated with Stillbirth

Infection	Organism	Vector or Animal Reservoir
Malaria	Plasmodium falciparum	Mosquito
Lyme disease	Borrelia burgdorferi	Tick
Relapsing fever	Borrelia duttonnii	Tick
Tick-borne relapsing fever	Borrelia recurrentis	Tick
African sleeping sickness	Trypanosoma brucei	Tsetse fly
Chagas disease	Trypanosoma cruzi	Triatomine (kissing bug)
Dengue fever	Dengue virus	Mosquito
Tularemia	Francisella tularensis	Tick or deerfly, animal carcasses, contaminated food/water
Listeriosis	Listeria monocytogenes	Domesticated animal products
Anthrax	Bacillus anthracis	Domesticated animals
Q Fever	Coxiella burnetti	Domesticated animals
Brucellosis	Brucella melitenses	Domesticated animals
Leptospirosis	Leptospira interrogans	Dogs, livestock, wild animals
Toxoplasmosis	Toxoplasma gondii	Warm-blooded animals
Lymphocytic choriomeningitis	Lymphocytic choriomeningitis virus	House mouse
Ljungan virus	Ljungan virus	Wild rodents (bank voles)
Streptococcus porcinus	Streptococcus porcinus	Swine

Adapted from: Goldenberg RL, McClure EM, Saleem S, Reddy U. Infection-related stillbirths. Lancet 2010;6736(09)61712–8.