Stillbirths' microbiology: a favorable time for *post-mortem* microbiology

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Summary

Post-Mortem Microbiology (PMM) aims to detect infections that could be a cause of stillbirth.

A newborn having no sign of life after delivery is defined as stillbirth. Different infections could cause a chain of events leading to stillbirth but the relationships between maternal infection and stillbirth are often not very clear; as a matter of fact, the positive serologic tests do not prove causality. Screening, prevention, and treatment of maternal infections are important to reduce the stillbirth risk. The identification of an infectious agent that causes stillbirth through PMM is a shared aim by microbiologists, pathologists and surgeons, and it is also the common goal in clinical and forensic autopsies. The aim of this paper is a review the major infections that lead to stillbirths.

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Introduction

Post-Mortem Microbiology (PMM) aims to detect infections that could be a cause of stillbirth.

A newborn having no sign of life after delivery is defined as stillbirth and it is one of the most common adverse pregnancy outcomes, with an estimated 3.2 million cases occurring each year worldwide. The incidence rates are as low as 3 per 1000 births in developed countries compared to rates approaching 45 per 1000 in some developing countries. The lower limits of gestational age range from 20 to 28 weeks [32,22]. Different infections could cause a chain of events leading to stillbirth but the relationships between maternal infection and stillbirth are often not very clear; as a matter of fact, the positive serologic tests do not prove causality. Infections could be a cause of stillbirth by three different mechanisms: i) a maternal infection which can lead to a systemic illness where the mother is severely ill [22,23,58]; ii) the placenta can be directly infected, resulting in reduced blood flow to the fetus and iii) for last the fetus may be directly infected through the placenta or membranes, resulting in damage of a vital organ such as the brain, lung, heart [34]. Several viruses and parasites and more than one hundred bacterial species are involved in intrauterine infections. These may be divided into infections of the fetal compartment, better known as ascending infections from the vagina to the cervix, or hematogenous through the placenta. The aim of this paper is to review the major infections that lead to stillbirths [40,53].

Virus infections

Parvovirus B19

It seems that viruses cause stillbirths, but a positive viral serologic result does not prove causation [32,23]. Nucleic acid and viral identification are only recently widely available. Several virus infections could be a cause of stillbirth. Parvovirus B19 causes a common disease called fifth disease, aplastic anemia in children with sickle cell disease, and childhood exanthem [12,43]. Parvovirus B19 may attack cardiac tissue and this mechanism could be a cause of stillbirth. Most cases of stillbirths occur in the second trimester and are associated with hydrops; however, this condition is associated with a quite low risk of stillbirth [60]. In Parvovirus B19 infection, the primary mechanism leading to stillbirth involves the predilection of the virus for bone marrow which

could concern fetal anemia and hydrops. The infections that result in stillbirth are generally acquired before 20 weeks of gestation [15,43,60].

Herpesvirus

Herpes simplex viruses (1/2) rarely are a cause of stillbirth. This occurs because the virus probably causes an intrauterine infection. Among the Herpesviridae family, Cytomegalovirus (CMV) infection is the most common congenital viral infection [43]. In the USA, 1–3% of pregnant women acquire CMV primary infection during pregnancy. Placental involvement is well-documented. Actually, it is not clear if CMV infection causes stillbirth and also the mechanism by which CMV can do it is not clear [8].

Rubella

It has been documented that the Rubella virus was first associated with a wide variety of anomalies and in 1941 was associated with congenital cataracts [1]. Rubella virus infects the placenta, enhancing the risk of stillbirth, and can do so without fetal spread. Maternal infection with rubeola was implicated, although rarely, as a cause of stillbirth, and the virus was isolated from fetal tissues [21,48].

Measles

Measles during pregnancy has deleterious effects on both the perinatal outcome and the mother. Gestational measles can potentially damage the fetus and is one of the serious complications that can occur during pregnancy [23]. Chiba et al. (2003) described four cases of measles infections occurring in pregnancy. Three of the four cases before 24 weeks of gestation ended in spontaneous abortion or stillbirth [9].

Hepatitis

Viral hepatitis is caused by infection with one of the several hepatotropic viruses [35]. Of these viruses, Hepatitis E Virus (HEV) infection has been associated with adverse outcomes during pregnancy, including maternal death, preterm birth, and stillbirth [41,46]. HEV often results in fulminant hepatic failure and death in up to 20% of cases. Other hepatitis viruses have not been implicated as a cause of stillbirth [42,57].

Ljungan virus

Ljungan Virus (LJV) infection is correlates with intrauterine fetal death, malformations, placental inflammation, myocarditis, encephalitis, and Guillain-Barré syndrome [26]. The lymphocytic choriomeningitis virus has also been implicated as a cause of stillbirth. LJV is found in 40% of stillborn but not in any of the tissue from normal pregnancies [62].

Enterovirus

The enterovirus family includes Enterovirus, Echovirus, Coxsackie virus, and Polio. Each can cross the placenta and cause fetal death. A histological exam of the placenta showed perivillous fibrin deposition and villous necrosis with inflammatory cell infiltration [31]. If Enterovirus causes stillbirth and the mechanism by which it does are not clear [5,16,43].

SARS-CoV-2

Pregnant women with Covid-19 are at increased risk of admission to an intensive care unit and are more likely to experience preterm birth [25,55]. There are growing arguments for an increased risk of fetal death and hypertensive complications of pregnancy [6,13]. Intrauterine growth restriction seems to be three times more frequent than in COVID negative patients. These anomalies could be explained by placental damage [29,55]. Regarding placental lesions in SARS-Cov-2 infection, some authors found no significant placental histopathological changes whereas others reported various lesions such as villositis, chorangiosis, chorioamniotis, fetal vascular malperfusion or fetal vascular thrombosis, villous edema and retroplacental hematoma as well as massive fibrin deposition along with chronic histiocytic intervillositis [6,13,36]. It is not clear whether SARS-CoV-2 is a cause of stillbirth [4,25,29].

Bacterial infections

Treponema and other spirochetal infections

The direct fetal infection by *Treponema pallidum* is the most common cause of fetal death because the placental infection is associated with decreasing blood flow to the fetus [32,31]. In southern African areas, about 51% of stillbirths were attributed to syphilis, while between 25% and 50% of all stillbirths are found in seropositive women [44]. Another spirochetal infection associated with stillbirth is Lyme disease, a systemic illness caused by the tick-borne spirochete *Borrelia burgdorferi*. Small series of stillbirths after maternal Lyme disease have been described [7]. Another spirochetal disease associated with adverse pregnancy outcomes, tick-borne relapsing fever, is caused by *Borrelia duttonii, which* has also been associated with preterm birth and low birth weight [32,31].

Q fever

Q fever is a rickettsial infection caused by *Coxiella burnetti* [47]. In humans, this infection is generally acquired by inhalation of infected aerosols during contact with meat products, although transmission has occurred by tick bite and ingestion of infected milk. Infections may be acute or persistent [28,30]. Q fever infection increases the risk of abortions in early pregnancy and prematurity or intrauterine fetal demise in late pregnancy [24,47]. Congenital malformations including hypospadias, bilateral renal agenesis, congenital hydronephrosis, syndactyly, adrenal hypoplasia, and rare cases reporting the death of the fetus have been described very rarely during pregnancy [30].

Listeria monocytogenes

Listeria monocytogenes is an excellent example of a hematogenous transmitted organism that causes fetal death. Infection is acquired by the mother, usually by eating contaminated food. *Listeria* infection occurs more frequently in the third trimester and in most cases, the maternal sickness is usually mild with non-specific symptoms (fever, flu-like syndrome, plus abdominal and back pain) or even asymptomatic [14,56]. The organisms are spread by hematogenous transmission to the placenta. The fetal and neonatal complications become less frequent as the gestational age increases. However, the complication can be represented by preterm birth, early-onset neonatal sepsis and fetal loss [27]. Segado-Arenas et al. (2018) reported a case of a late stillbirth secondary to maternal chorioamnionitis [51]. *Listeria monocytogenes* was isolated from the amniotic fluid and the fetal pleural fluid. Although listeriosis could rarely lead to stillbirth, Mylonakis et al. (2002) reported a series of cases of 11 maternal listeriosis with two stillbirths secondary to the infection acquired in the second trimester of gestation [14,54].

Chlamydia trachomatis and Neisseria gonorrhoeae

C. trachomatis is the most common sexually transmitted bacterial pathogen. Although *Chlamydia trachomatis* and *Neisseria gonorrhoeae* have been found in internal organs at the time of stillbirth autopsy, neither appears to be a significant factor in stillbirths. Bacteria also reach the fetus through the placenta [20,38,45].

Other bacteria

Intrauterine bacterial infection has also been related to fetal death. *Ureaplasma urealyticum* and *Mycoplasma hominis,* including a large variety of other bacteria such as *Bacteroides* spp., *Gardnerella* spp., *Mobiluncus* spp., various enterococci, can cause infections that lead to stillbirth [32,31]. The organisms that have low virulence can stay in the uterus for months before precipitating preterm labor. Organisms such as group B streptococci and *E. coli* have crossed intact fetal membranes and caused amniotic fluid infection [50,23]. Whether the amniotic fluid infection occurs in the presence of intact membranes or follows membrane rupture, the organisms may be aspirated, enter the fetal lung, and cause severe infection. Whether the fetus is stillborn with congenital pneumonitis or is born alive with pneumonia may depend on the length of time between infection and delivery. Births before 28 weeks are strongly associated with amniotic fluid infection [37,40,58]. For example, several autopsy studies cultured organisms such as group B streptococcus, *E. coli,* and *Klebsiella* and enterococci from fetal heart blood, liver, lung, and brain. Group B streptococcal infection often occurred so rapidly that there was a minimal fetal inflammatory response [10]. Many of these infections occurred in the presence of intact membranes. They suggested that, when the organisms enter the uterus after membrane rupture, rapid bacterial replication occurs in the amniotic fluid and fetus with little infection in the membranes themselves. Christensen *et al*. noted that fetal mortality associated with group B streptococcal infection often occurred so rapidly that there was a minimal fetal inflammatory response [32,31]. Tuberculosis is among the leading causes of death among infectious diseases. Active tuberculosis increases the risk of pregnancy complications, but the association between Latent Tuberculosis Infection (LTBI) and pregnancy outcomes is unknown (Walles J. et al, 2022).

Parasitic infections

Plasmodium and Trypanosoma

The impact of malaria on pregnancy outcomes varies based on the type of malaria. *Plasmodium falciparum* has been most implicated in stillbirth; recently, also *P. vivax* has been associated with stillbirth [49,61]. More than 40% of all births worldwide occur in areas with endemic malaria and in women living in endemic areas, placental malaria occurs in 16–63% of maternal infections [39]. Several histological changes in infected placentae have been described, including the infiltration of mononuclear cells, deposition of malaria pigment, thickening of the trophoblast basement membrane, syncytial knotting, and complement deposition [2,59]. Histologically, placental malaria is characterized by parasites and leukocytes in the intervillous space and pigment within macrophages. Lymphocyte and macrophage accumulation, thickening of the trophoblast basement membrane, and increased expression of various proinflammatory cytokines impede maternal blood flow through the placenta [3,61]. So, malaria is an important cause of stillbirth throughout endemic areas. Also, the parasites *Trypanosoma brucei* have been demonstrated in the placentas of stillborn [19]. If the mother is infected during pregnancy, toxoplasmosis can be transmitted to the fetus via the placenta. Disseminated toxoplasmosis may cause fetal death [52].

Conclusions

Infections could be the cause of stillbirths by several mechanisms including direct infection, placental damage, and severe maternal illness. Various organisms have been associated with stillbirth, including many bacteria (such as Streptococcus agalactiae), viruses (such as Parvovirus B19), and protozoa (such as malaria) [17,32,31]. In some contests, the stillbirth rate is high and the infection-related component so great that achieving a substantial reduction in stillbirth should be possible by reducing maternal infections [23]. However, because infection-related stillbirth is uncommon in developed countries, and because those that do occur are caused by a wide variety of organisms, reducing this etiologic component of stillbirth will be difficult. Screening, prevention, and treatment of maternal infections are important to reduce stillbirth risk. Identifying an infectious that cause stillbirth using PMM is a shared aim by microbiologists, pathologists and surgeons, which is also the common goal in clinical and forensic autopsies [11,17,18,33]. Moreover, in the forensic setting, it may have legal implications. Therefore, PMM is an integral part of the evaluation of any stillbirth death.

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