

# “The Infectious Origins of Stillbirth” (2003) by Robert L. Goldenberg and Cortney Thompson

In September 2003, Robert L. Goldenberg and Cortney Thompson published the article “The Infectious Origins of Stillbirth” in the American Journal of Obstetrics and Gynecology. In the article, the authors conducted a literature review of articles from the US National Library of Medicine database to review the relationship between perinatal infections, which are infections around the time of birth, and the occurrence of stillbirth. Stillbirth is the death of a fetus in the uterus after at least twenty weeks of pregnancy. Infectious disease can cause or increase the risk of stillbirth in several ways, by causing illness in the pregnant person, damaging the placenta, or directly infecting the fetus. Infectious agents can be viruses, bacteria, or protozoa. Rates of infectious disease and stillbirth are both higher in developing countries than in developed ones, and the authors state that stillbirth due to infectious disease is also higher. “The Infectious Origins of Stillbirth” offers a comprehensive review of the information available on how infections can lead to stillbirth, providing a foundation for further research.

Stillbirth is the death of a fetus before or during delivery, after at least twenty weeks of pregnancy. In their article, Goldenberg and Thompson use the terms stillbirth, fetal death, and intrauterine fetal death interchangeably. According to them, the rates of stillbirth differ between developed and developing countries. In developed countries, rate of stillbirth can be as low as three per 1000 births, whereas in developing countries it can be as high as ninety per 1000 births. Professionals commonly discuss stillbirths in the context of what causes them, such as problems with the development of the fetus, problems with the transfer of nutrients to the fetus in the uterus, or infection. The much higher rate of stillbirth due to infection in developing countries is likely due both to the higher frequency of exposure to bacteria, viruses, and protozoa, which are microscopic single-celled organisms, and to reduced access to adequate medical care.

At the time of publication, both Goldenberg and Thompson were researchers at the Department of Obstetrics and Gynecology at the University of Alabama at Birmingham, or UAB, in Birmingham, Alabama. Goldenberg joined the faculty of UAB in 1976, after which he served as Director of the UAB Center for Women’s Reproductive Health, Director of the UAB Center for Obstetric Research, and as chairman and Charles E. Flowers Endowed Chair of the UAB Department of Obstetrics and Gynecology. Since 2008, he has been a Professor Emeritus of the UAB Department of Obstetrics and Gynecology. At the time of publication, Thompson was a researcher in the Department of Obstetrics and Gynecology at UAB.

The authors conducted a literature review to compile information available on the effect of infection and infectious disease on stillbirth. They used textbooks, searches on the database MEDLINE, and a list of publications related to the subject to identify relevant English language publications on the topic. The article provides an examination of what the medical community knew about perinatal infection and its impact on stillbirth in 2003.

The article consists of four sections, two of which, the unnamed introduction and “Specific infections related to stillbirth,” have several sub-sections. In the unnamed introduction, the authors define stillbirth and discuss the connection between infection in the pregnant person and stillbirth. In the second section, “Specific infections related to stillbirth,” the authors discuss five categories of infections, including viruses, bacteria, and parasitic protozoa. Parasitic protozoa, which are very small organisms that live inside bigger animals, like humans, cause infections such as malaria and toxoplasmosis. In the third section, “Prevention of infection-related stillbirth,” the authors discuss options and strategies for medical treatment of infections to prevent stillbirth. In the fourth and

final section, "Comment," the authors state that the primary causes of stillbirth by infection differ between developed and developing countries, but that physical barriers between the fetus and the rest of its parent's body often protect it.

In the unnamed introduction, the authors talk about rates of stillbirth and discuss the relationship between maternal infection, which is an infection affecting the pregnant person, and stillbirth. They state that maternal infections can directly infect the fetus, damage the placenta, cause severe maternal illness, or cause preterm labor, all of which may lead to fetal death. The placenta is a temporary organ in the uterus that helps to provide the developing fetus with nutrients and is very important to fetal health during pregnancy. In the case of maternal illness, the authors state a fetus may die because of high stress to the pregnant person's body, such as high fever, respiratory distress causing trouble breathing, or other bodily reactions to the illness, even if neither the fetus nor the placenta are infected with the agent causing the illness. In other cases, the placenta may become infected, suffering damage. According to the authors, the stillbirths associated with maternal malaria infection are likely due to damage to the placenta. Infections may also pass through the placenta or membranes around the fetus, infecting it, and could damage a vital organ such as the lung, liver, heart, or brain, causing death immediately or later on during pregnancy. Finally, an infection may trigger preterm labor, or labor before the fetus is developmentally ready to be born, in which case the fetus cannot live outside the uterus and dies before or during delivery.

The second section, "Specific infections related to stillbirth," consists of six smaller sections, which are "Spirochete infections," "Malaria," "Toxoplasmosis," "Q fever," "Viral diseases," and "Bacterial infections." In each, the authors discuss pathogens, which are the specific organisms which cause the infections, along with how the pregnant person could acquire the infection, the effects of the infection, and how it might endanger the fetus. Spirochetes are spiral-shaped motile bacteria, some of which are serious pathogens for humans, causing diseases such as syphilis, Lyme disease, and African tick-borne relapsing fever. The authors examine the case of *Treponema pallidum*, the spirochete that causes syphilis, which is transmitted mainly through sexual contact. Spirochetes are able to cross the placenta and infect the fetus at fourteen weeks gestation. According to Goldberg and Thompson, if a spirochete infects the fetus, about forty to fifty percent will die in utero, with another thirty to forty percent being born alive but having signs of syphilis. The authors mention that the rate of syphilis is higher in developing countries than in developed ones and that, for some infections, such as African tick-borne relapsing fever, it is difficult to determine whether the infection causes stillbirth due to the infection's prevalence in a population.

The authors then discuss malaria. In humans, parasitic protozoa in the genus *Plasmodium* cause malaria. Mosquito bites transmit those protozoa, which are microscopic, single-celled organisms that can be free-living, meaning they don't need to live in a host, or parasitic, meaning they do. More than forty percent of all births worldwide occur in areas where malaria is prevalent. According to the authors, malaria is particularly harmful to pregnant people because it significantly increases the risk of moderate to severe maternal anemia, or the pregnant person having too little iron in their blood, as well as preterm birth and fetal growth restriction, which is when the fetus does not grow enough in the uterus. The authors speculate that malaria may more directly cause stillbirth by the parasites which cause malaria infecting the placenta. In malarial placental infection, the placenta can become damaged or not develop properly, leading to restricted transport of oxygen and nutrients to the fetus. It can also prevent antibodies from reaching the fetus. The authors then discuss another protozoan parasite, *Toxoplasma gondii*, which causes toxoplasmosis. The parasite typically infects humans when they eat undercooked meat or scoop cat litter. *Toxoplasma gondii* can be transmitted through the placenta to the fetus, and can damage the brain or cause fetal death. However, stillbirth due to *Toxoplasma* infection is rare.

The authors complete "Infections related to stillbirth" with two subsections, which are "Viral diseases" and "Bacterial diseases," in which they discuss multiple viruses and bacteria which may be linked to stillbirth. In "Viral diseases," they consider nine kinds of viruses. They state that for most viruses, it is difficult to determine that an infection causes stillbirth. The authors explain the difficulty in both identifying a specific virus in a patient and determining whether a virus directly causes any complications in pregnancy. In some cases, such as in pregnant people who have the human immunodeficiency virus, or HIV, the viral infection is linked to a higher risk of stillbirth.

However, the authors qualify that the risk of stillbirth in patients with HIV is less likely due to the virus itself and more likely associated with other health conditions the patients may contract due to having HIV. The authors also discuss several common childhood illnesses, such as chickenpox and measles, and state that immunity in the pregnant person decreases risk to them and to the fetus, meaning that a pregnant person who has previously been infected with a virus, like chickenpox, or who has received a vaccine against it is less likely to become sick, and the infection is less likely to reach or affect the fetus. Like other infections they discuss, such as spirochete infection, fetal mortality increases with viral infections that can cross the placenta and directly infect the fetus, such as parvovirus.

In "Bacterial infections," the authors claim that a review of the literature on infection and stillbirth points to a wide variety of bacteria that infect the placenta, membranes surrounding the fetus, or the fetus itself and that have been associated with stillbirth. Goldenberg and Thompson divide bacteria into two categories, bacteria that reach the fetus through ascending bacterial infections and bacteria that reach the fetus through the placenta. The authors define ascending bacterial infections, which occur when bacteria ascend from the vagina and infect the uterus during early pregnancy or reside in the uterus before pregnancy. Those infections enter the amniotic fluid, which is the fluid surrounding a fetus, either through intact amniotic membranes or after the membranes rupture. The most common pathway of attack is by way of the fetal lung through fetal breathing of contaminated amniotic fluid. The authors then describe the second mechanism of infection, which is by blood transfer through the placenta. According to the authors, microbes generally appear to enter the fetus through the umbilical vein, which carries oxygenated blood from the placenta to the fetus. Throughout the section Infections related to stillbirth, the authors refer to the mechanisms by which infections may cause stillbirth. In many cases, the effect of infection is more severe if it is the first time that the pregnant person encounters the infection, if the infection happens early during pregnancy, or if the infection reaches the fetus itself.

In the final two sections, "Prevention of infection-related stillbirth" and "Comment," the authors discuss the prevention of infection-related stillbirth and summarize the article. Goldenberg and Thompson claim the largest potential benefit to the prevention of infection-related stillbirth in developed countries would be to reduce the stillbirths associated with bacterial intra-amniotic infections. According to the authors, in a number of geographic areas, health care providers do not screen for or treat group B *Streptococcus*, which is a type of bacteria that around twenty-five percent of women carry and can be easily treated with antibiotics. However, in many developing countries, infectious disease has a much higher prominence and effect during pregnancy, and the stillbirth rate is higher in many countries because of that. 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.

As of March 2022, the article "Infectious Origins of Stillbirth" has been cited over 400 times. Clinical researchers in developing countries, which have a high rate of stillbirth due to bacterial infection, have cited it especially frequently. The article provides essential information about perinatal mortality that allowed for much further research in the area of stillbirth and infectious disease.

## Sources

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