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Role of contaminated water for stillbirths in pregnant women

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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. Every country has to develop and implement a plan to improve maternal and neonatal health that includes a reduction in stillbirths, and to count stillbirths in their vital statistics and other health outcome surveillance systems. We also ask for increased investment in stillbirth-related research, and especially research aimed at identifying and addressing barriers to the aversion of stillbirths within the maternal and neonatal health systems of low-income and middle-income countries. Screening, prevention and treatment of maternal infections are important to reduce stillbirth risk.

Keywords: Infection; Contaminated water; stillbirth

1. Introduction

Many developing countries, although still besotted with communicable diseases are passing through a gradual and progressive transformation in the health scenario as a result of improvement in health care scenario and advances in medical technology in preventative and curative aspects. Stillbirths are frequently categorized by presumed etiology. The most adverse outcome of stillbirth is unlike any other form of grief the months of excitement and hope, preparation, eager questions, and the drama of labour - all magnifying the shocking incomprehension of giving birth to a baby bearing no signs of life. Approximately 3 million third-trimester stillbirths occur worldwide each year, means that 11 sets of parents every day will take home their newborn baby in a coffin. The too-common stigmatisation of women who have given birth to a dead baby is unfair, cruel, and not based on facts. The relationships between infection and stillbirth may be unclear for several reasons. Stillbirth is the colloquial term commonly used term for fetal death, and is the term used in this series to refer to both early and late fetal deaths. But unknown, percentage of stillbirths may be caused by various types of maternal or fetal infections. Recent global estimates suggest that at least 3.2 million babies are born dead each year. Whilst the highest absolute numbers of stillbirths occur in South Asia, driven by the large population size of that region. This review article provides an insight into the role of contaminated water in causing stillbirths in pregnant women.

1.1 Definition

WHO defines Stillbirth as a fetal death late in pregnancy, and individual countries define the gestational age at which a miscarriage becomes a stillbirth. The perinatal period is defined as 22 weeks or more of gestation (154 days) or, if the gestational age is unknown, it includes infants with a birth weight of 500 g or more and ends 7 days after birth. For international comparison, stillbirths are defined as infants born showing no signs of life in the perinatal period. According to the *1992 Revision of the Model State Vital Statistics Act and Regulations* recommends the following definition ‘‘Fetal death’’ means death prior to the complete expulsion or extraction from its mother of a product of human conception, irrespective of the duration of pregnancy and which is not an induced termination of pregnancy. The death is indicated by the fact that after such expulsion or extraction, the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. Heartbeats are to be distinguished from transient cardiac contractions;

respirations are to be distinguished from fleeting respiratory efforts or gasps. Stillbirth, defined as no sign of life in a neonate at delivery, is one of the most common adverse outcomes of pregnancy.

2. Stillbirth history and Geography

100 years ago stillbirth rates as high as 50 per 1000 births were frequently recorded, but rates have fallen to fewer than five per 1000 - a reduction of more than ten times. Many of the interventions that prevent stillbirth, including antenatal care, admission to hospital for delivery, and use of caesarean section in cases of fetal distress were introduced. Reductions in rates, however, have not been uniform across all types of stillbirth. It has been observed that term or intrapartum stillbirths are infrequent and most now occur preterm in the antepartum period. Thus, the downward trajectory of stillbirth rates has substantially slowed, in part because little or no improvement has been made in antepartum stillbirth rates.

3. Classification

Stillbirths can be sub classified according to the gestational age at birth, typically into early stillbirths (20–28 weeks gestation) and late stillbirths (after 28 weeks). Although this division is somewhat arbitrary, this stratification allows for fairly reliable international comparison of late losses, and allows stillbirths to be divided into those that are difficult to prevent (i.e., early losses) and those that are potentially preventable (i.e., late losses). Stillbirths are also subclassified by whether death occurred before or after the onset of labour - termed antepartum and intrapartum, respectively.

4. Mechanism

Infection can cause stillbirth by several mechanisms. Maternal infection might lead to systemic illness with the mother becoming severely ill (e.g., severe influenza), and the fetus might die because of high maternal fever, respiratory distress, or other systemic reactions, without organisms transmitted to the placenta or fetus. Alternatively, the placenta might be directly infected, resulting in reduced blood flow to the fetus (e.g., malaria), or the fetus might be directly infected with damage to a vital organ. If infection occurs early in gestation, the fetus might not die immediately but development of a congenital anomaly could lead to fetal death at a later stage of pregnancy. Last, a maternal infection of the genital tract or elsewhere might precipitate preterm labour that the fetus is unable to tolerate. There are at least 40 organisms with sufficient evidence to be implicated as a cause of fetal death, including many different bacteria, viruses, parasites, and fungi enlisted in table 1. Although every organism is not examined in this Review, we have tried to draw attention to those that are important numerically or those for which evidence suggests that further research could be beneficial. Many infectious causes of stillbirth are borne by animals or vectors. First, infection is often not apparent from the case history or physical examination of the mother or fetus. Routine histological 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 histological 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 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.

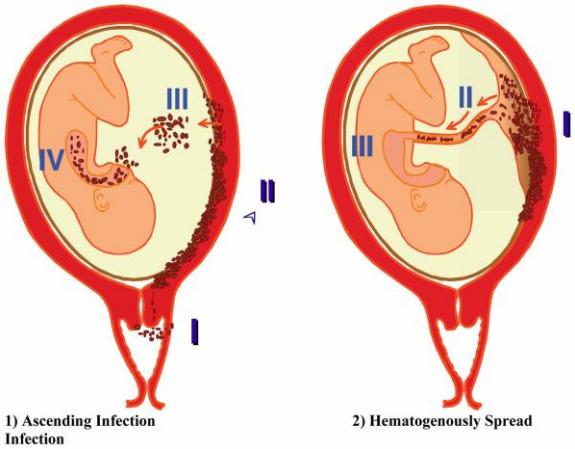

Figure: 1: Pathways to placental and fetal infection

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

Table 1: List of Water-borne Diseases

a) Bacterial Diseases and Contaminants

Aeromonas hydrophila	Cholera	Escherichia coli 0157:H7 / "E. coli"	Leptospirosis	Pontiac Fever
Burkholderia cepacia complex	Cyanobacteria	Folliculitis	*Mycobacterium avium* complex	Pseudomonas
Buruli Ulcer	Dental Caries	Hot Tub Rash	*Mycobacterium ulcerans*	*Salmonella typhi*
Campylobacteriosis	Dermatitis	Legionnaires' Disease	Otitis Externa	Shigellosis
Chlamydia trachomatis	Diarrhea	Legionellosis	Plesiomonas shigelloides	*Staphylococcus aureus*
Swimmer's Ear	Typhoid Fever	*Vibrio parahaemolyticus*	*Vibrio vulnificus*	Trachoma
Vibrio cholerae				

b) Parasitic Diseases and Contaminants

Acanthamoeba	Cryptosporidiosis	*Fasciola gigantica*	Hookworm	Naegleria Infection
Amebiasis	Cryptosporidium	*Fasciola hepatica*	Head Lice	Onchocerciasis
Ascariasis	Cyclosporiasis	*Fasciolopsis buski*	Lymphatic filariasis	Pinworms
Ascaris lumbricoides	Diarrhea	Giardia	Malaria	Pubic Lice
Bilharzia	Dracunculiasis	Giardiasis	Microsporidiosis	River Blindness
Body Lice	*Dracunculus medinensis*	Guinea Worm Disease	Microsporidium	Scabies
Cercarial Dermatitis	*Entamoeba histolytica*	Helminthiasis	Naegleria fowleri	Schistosomiasis
Soil transmitted helminths	Swimmer's Itch	*Toxoplasma gondii*	Toxoplasmosis	*Trichuris trichiura* (whipworm)

c) Viral Diseases and Contaminants

Adenoviruses	Hepatitis A	Rotavirus
Astrovirus	Hepatitis E	St. Louis Encephalitis
Coxsackievirus (A16, B) (Enterovirus)	Japanese Encephalitis	Viral Gastroenteritis
Dengue Fever	La Crosse Encephalitis	West Nile Virus
Diarrhea	Meningitis, Viral	Western Equine Encephalitis
Eastern Equine Encephalitis	Molluscum contagiosum	Echovirus (Type 9, 13, 30) (Enterovirus)
Norovirus	Enterovirus	Rift Valley Fever

d) Chemical Diseases and Contaminants

Arsenic	Ethylbenzene	Methaemoglobinaemia
Atrazine	Fluoride	Nitrate
Benzene	Fluorosis	Radionuclides
Chromium	Lead	Radium
Copper	Mercury	Radon

e) Other Diseases, Contaminants, and Injuries

Algal Blooms, Harmful (HABs)	Harmful Algal Blooms (HABs)	Ringworm
Drowning	Injury, Water-related	Tinea
Entrapment	Marine Toxins	Toxins, Marine

5. Contaminated water and Stillbirth in pregnant women

Table 2: List of organism with their maternal disease and their possible effects on stillbirth [16]

Organism	Maternal Disease	Comment
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
Leptospira interrogans	Leptospirosis	Confirmed as cause of stillbirth but not common
Other bacterial infections usually transmitted transplacentally include: *Tularemia, Tuberculus Brucellosis, Clostridia, Typhoid, Anthrax, Streptococcus pseudoporcinus, Agrobacterium radiobacter, Pseudomonas,* etc.	Variable	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		Confirmed as cause of stillbirth but of unknown importance
Enterovirus		
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
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	Acquiredimmunodeficiency 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
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
Ascending Bacterial Infections		
Ureaplasma urealyticum	Generally asymptomatic	Confirmed as a cause of stillbirth
Mycoplasma hominus		
E coli		
group B *Streptococcus*		
Klebsiella		
Bacteroidaceae		
Neisseria gonorrhoeae		
Chlamydia trachomatis		

5.1 Syphilis

Of all potential infectious causes of stillbirth worldwide, syphilis stands out because the disease causes a large number of stillbirths but is highly preventable. Spirochaetes can cross the placenta and infect the fetus, with risk of fetal infection related to the stage of maternal syphilis. If the mother is infected but untreated, about 40% of fetuses will die in utero and another 30–40% will be born alive but have congenital syphilis. More than 1 million cases of congenital syphilis occur worldwide every year. The most common cause of fetal death seems to be placental infection with decreasing blood flow to the fetus, although direct fetal infection also has a role. Most studies report syphilis to have a relative risk of stillbirth of however, in a Tanzanian study, the relative risk was 18 for women with active syphilis. In some areas of sub-Saharan Africa, 25–50% of all stillbirths are associated with syphilis. Syphilis also contributes to stillbirths in other areas of the world including Russia, Asia, and South America. Stillbirths due to syphilis should be easy to eliminate. Within a functioning health system, screening of pregnant women for syphilis is feasible, and once disease is diagnosed, treatment is easy and inexpensive. Women who have been treated for syphilis have a similar or slightly greater stillbirth risk than do women who are not infected. The reasons for the present failure to eliminate congenital syphilis, especially in sub-Saharan Africa, include poor access to prenatal care or use of such services, and failure to provide appropriate treatment for syphilis because of lack of resources, poorly functioning supply systems, and other priorities such as HIV screening and treatment. Consequently, point-of-care rapid testing and treatment could be the most cost-effective method to reduce adverse pregnancy outcomes associated with syphilis. Schmid and colleagues converted the fetal orneonatal consequences of maternal syphilis into disability adjusted life-years.

5.2 Lyme disease

Systemic illness caused by the tick-borne *Borrelia burgdorferi*, was first associated with stillbirth in 1987. Small series of stillbirths associated with maternal Lyme disease have been reported, with most fetal deaths occurring in the midtrimester. Spirochaetes have been found in fetal liver, spleen, kidney, and brain. However, large-scale serological studies have shown that few stillbirths are associated with Lyme disease except in highly endemic areas. In Tanzania, more than 30% of adults are seropositive for *B burgdorferi* compared with 2% in the USA and Norway, but whether Lyme disease is an important cause of stillbirths in African settings is unknown. Another spirochaetal disease associated with adverse pregnancy outcomes, mainly in sub-Saharan Africa, is tick-borne relapsing fever, caused by *Borrelia duttonii*.

5.3 Campylobacteriosis

Campylobacter is a Gram-negative curved rod. Several species are pathogenic in man. *C. jejuni* is found in the intestinal tracts of animals (especially chickens) and in untreated water. It's a very common cause of diarrhea accompanied by fever. This organism thrives in a reduced oxygen environment and is inhibited by acid, salt and drying.

Most cases of bacteraemia with septic abortion or premature delivery were caused by C. *fetus* as reviewed by Gribble *et al*. Although pregnant women are not at increased risk of becoming infected with *C. jejuni*, if they do get sick, the infection may spread to the placenta. *Transplacental spread from systemic maternal infection has resulted in abortion, stillbirth, and early neonatal meningitis.* A case report of a 19 year old patient with 27 weeks pregnant when admitted to hospital with fever, chills and premature labours. The following day she aborted, Campylobacter coli was isolated from blood cultures, maternal placenta, amniotic fluid and from the ear, nose and pharynx of the stillbirth. Clinical investigations revealed pain on deep pressure on both costovetebral areas. The pathological-anatomical

examination of the corpse (890 gm, 36 cm) of the male fetus revealed disharmonic hypotrophy.

5.4 Rubella

Maternal rubella was associated with congenital cataracts by Gregg in 1941. Subsequently, other abnormalities such as major cardiac defects have been recorded, some of which result in stillbirth later in pregnancy. Rubella also infects the placenta, increasing the risk of stillbirth, and can seemingly do so without fetal spread. Maternal infections with mumps and rubella (measles) have both been implicated as causes of stillbirth, and both viruses have been isolated from fetal tissues. In Guinea-Bissau, occurrence of stillbirth increased by four to nine times if the mother was infected with measles during her pregnancy.

5.5 Chickenpox

Varicella (chickenpox) infections during pregnancy can cause maternal pneumonia, placing infected women at risk for death as well as stillbirth. The virus also occasionally crosses the placenta and attacks the fetus directly. Such findings confirm the association between maternal infection with common childhood viruses and increased risk of stillbirth.

5.6 Cholera

Cholera in the third trimester was associated with significantly greater dehydration and stool output than in the second trimester, or in non-pregnant controls. 18 of 36 third-trimester patients had stillborn infants early in the course of the disease. Fetal deaths were attributed to the effects of hypoxia and acidosis. Fetal wastage due to cholera can probably be effectively reduced only by preventing maternal infection.

5.7 Hepatitis E

Since vertical transmission risk was reported for hepatitis E virus the death of the new born and also the stillborn babies were likely due to the mother-child transmission by the mother who presented an acute hepatitis either during delivery or during the third trimester of pregnancy. In addition to the observation that a decrease in cellular immunity during pregnancy; coupled with high levels of steroid hormones, may influence hepatitis E viral replication to cause the reported high mortality.

5.8 Listeriosis

These bacteria are widespread in nature, being found in soil, decaying vegetation and the bowels of many mammals. People are probably frequently exposed to Listeria, with only mild illness resulting. However, infection is more serious when it occurs in new born babies, the elderly, immune suppressed people and pregnant women. Pregnant women may have relatively mild symptoms (fever and aches) and make a quick recovery. However, they may transfer the infection to their unborn child who may be stillborn or born very ill.

5.9 Arsenic Contamination

No conclusive information on pregnancy outcome and infant mortality in relation to arsenic levels in drinking water is available in literature as a few studies included individual assessment of arsenic concentrations in all water sources used during pregnancy. In an ecological study carried out in Chile, stillbirths (rate ratio1.7: 95%CI: 1.5. 1.9), neonatal and post neonatal infant mortality rates were found to be increased in the high arsenic exposure city of Antofagasta as compared with the low exposure city of Valparaiso. A study conducted in Bangladesh showed an increased risk of stillbirth for women with current arsenic level ≥100µg/l, although the risk estimates were smaller. One earlier cross-sectional study from Bangladesh compared rates of spontaneous abortions, stillbirths and preterm delivery between 96 women in one village who were exposed to ≥100µg/l arsenic to rates in 96 women in another village who were exposed to less than 20 µg/l and showed two to three times higher rates among exposed women. Increased risk of spontaneous abortion, stillbirth, preterm birth and neonatal death at elevated water arsenic concentrations were indicated in three, fairly small, studies two in Bangladesh and one in West Bengal, in which 192, 533, and 202 women of childbearing age, respectively, were interviewed about previous pregnancies.

Though the relation has not been studied in countries of low and middle income, in high-income countries, one of the best described relations of a virus with stillbirth is for parvovirus B19. Parvovirus causes the common child hood rash erythema infectiosum, and also causes aplastic anaemia in children with sickle cell disease. Parvovirus can cross the placenta and preferentially attacks erythropoietic tissue, causing severe fetal anaemia, non-immune hydrops, and fetal death. Parvovirus can also cause stillbirth by directly attacking fetal cardiac tissue, resulting in cardiac damage without associated hydrops. Previous parvo virus infection elicits an antibody response that protects against subsequent maternal and fetal infection. However, even with a new maternal parvovirus infection, the risk of stillbirth is small. However, findings of a study in Sweden that used PCR for viral DNA to confirm parvovirus infection showed that 15% of all stillbirths were attributed to parvovirus.

Newly described viruses are also being associated with stillbirth. For example, Ljungan virus, a picornavirus of bank voles, was originally isolated in the Ljungan Valley in Sweden and has since been reported in Denmark and the USA. Infection with the

virus was recorded in 40% of stillborn babies in a small study of pregnant women, but not in any tissues from normal pregnancies. The overall importance of this infection as a cause of stillbirth in any location is unknown.

6. Conclusion

Prevention of stillbirths associated with ascending bacterial infection in the presence of intact membranes has proven elusive. No strategies - including antibiotic prophylaxis - seem to prevent intrauterine infection or associated stillbirths, although antibiotic treatment targeting bacterial vaginosis could be beneficial in some women. In women with preterm premature rupture of membranes, prophylactic antibiotics reduce histological chorioamnionitis, but have not yet shown a similar reduction in occurrence of stillbirths. Although viruses clearly cause stillbirths, the overall nature of this relation is not well studied, especially in countries of low and middle income. The complexity and expense of culturing of most viruses, and the technical difficulty and expense associated with PCR for identification of viral DNA or RNA have hampered research. Consequently, the importance of maternal viral infection as a cause of stillbirth in most areas of the world is unknown. Descriptive epidemiology provides the foundation for all further long term focused analytical studies (case control, cohort) for risk factors, identification and quantification along with possible clues to the aetiopathogenesis. The next appropriate strategy is to develop intervention methods and conduct will designed experimental epidemiological researches towards identifying the optimum therapeutic modalities and strategies towards control of diseases.

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