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Stillbirth in Developing Countries: A review of causes, risk factors and prevention strategies

Elizabeth M. McClure and **Robert L. Goldenberg**

Abstract

In reviewing the research on stillbirth in developing countries, it becomes clear that because almost half of the deliveries in these settings occur at home, under-reporting of stillbirths is a significant problem, and reliable data about rates and causes are unavailable in some areas of the world. Nevertheless, of the estimated 3 million stillbirths which occur yearly, the vast majority in developing countries, with rates in many developing countries ten-fold higher than elsewhere. Classification systems have been adapted for developing countries; however, there is not a standard international system, nor is there agreement about stillbirth definitions making comparisons of cause of stillbirth over time or between sites problematic. From available data, prolonged and obstructed labor, and various infections all without adequate treatment, appear to account for the majority of stillbirths in developing countries. Strategies that have effectively reduced stillbirth in developed countries have had mixed results in developing countries or have not yet been tested; however, identification and treatment of infections such as syphilis has been shown effective in reducing stillbirth risk, while strategies to improve obstetric care have not been widely evaluated. Despite the large number of stillbirths worldwide, the topic of stillbirths in developing countries has received very little research, programmatic or policy attention. Better access to appropriate obstetric care, especially during labor, should reduce developing country stillbirth rates dramatically.

Keywords

stillbirth; developing countries; perinatal mortality

Introduction

Developing countries represent 98% of estimated 3.3 million stillbirths, which occur annually.(1) While many developed countries rates have stillbirth rates as low as 3–5 per thousand births, most developing countries have rates that are ten-fold higher.(2) Reductions in stillbirth rates in developed countries are primarily due to the reductions that occurred in intrapartum stillbirth rates. (4,5) Increased access to obstetric services -including better intrapartum fetal monitoring - and to cesarean sections appear to be associated with these decreases in stillbirth.(6,7)

In developing countries, the causes of stillbirth, generally similar across regions, include maternal infection, fetal asphyxia, trauma, congenital abnormalities, fetal-maternal hemorrhage, and a variety of medical conditions of the mother.(2) Because there is not a standard international system for defining stillbirth, comparisons over time and between

Corresponding Author: Elizabeth M. McClure, Research Triangle Institute, 3440 Cornwallis Road, Durham, NC 27709, Phone: 919-316-3773, Fax: 202-354-4787, mcclure@rti.org.
Robert L. Goldenberg, Drexel University, Philadelphia, PA, rgoldenb@drexelmed.edu

geographic areas is problematic and, even using the available classification systems, the cause of most stillbirths remains unknown.

Global Stillbirth Rates

Most countries do not include stillbirth in their vital statistics reporting system, where available, and when stillbirth is included, these rates are generally underreported for various reasons. (9) This is especially true at the lower gestational ages or birth weights. (10) However, even when stillbirth registration is excellent, variations between the lower birthweight and gestational age cutoffs used to define stillbirth make comparisons between countries difficult, and especially comparisons between developed vs. developing countries. For example, states in the United States generally use a lower gestational age limit of 20 weeks or about 350g. (2) Since gestational age dating is often inaccurate, many developing countries use a birthweight cutoff as part of their stillbirth definition. Furthermore, because even live-born infants weighing <1000g frequently do not survive, many developing countries use 1000g as the lower weight limit for defining a stillbirth. (2) In the United States, half of all stillbirths occurring at greater than 20 weeks gestation occur at less than 28 weeks or less than 1000g. (10) Assuming that this relationship holds true elsewhere, when 1000g is the lower birthweight cutoff, by United States standards, the stillbirth rates will be underestimated by half in those geographic areas.

However, recently, efforts using existing data systems have been made to evaluate stillbirth rates, by modeling to obtain standard gestational age and birthweight cut-offs. Stanton et al estimated a stillbirth rate of 25.5 per 1000 births for developing countries in the year 2000, with sub-Saharan Africa representing the highest rate (32.2 per 1000 births or a total of 889,697), followed by South Asia (31.9 per 1000 or a total of 1,286,231 births). (1) A recent study of stillbirths in Zambia found stillbirth rates to be 32.9 per 1000 births. (11) In Latin America, with both middle-income and lesser-developed countries, stillbirth rates generally range from 15 to 25/1000 births. (12) Most countries in the Middle East have rates of 10 to 20/1000. (1) South Asia has the world's largest population and highest number of stillbirths, with rates generally 25 to 40/1000 births. (1) For example, a prospective study of middle-class women in Hyderabad, Pakistan with good access to health care, found stillbirth rates of 33.6 per 1000 births (13), while a study conducted at a referral hospital in Karachi reported a stillbirth rate of 73.4 per 1000 births. (14) In a prospective community-based, multi-country study, conducted in countries in South Asia, Latin America and Africa, stillbirth rates ranged from 9 in Argentina to 34 per 1000 in Pakistan. In this study, nearly 80% of the stillbirths had no signs of maceration and most likely represented intrapartum stillbirths.(15) In contrast, a multi-country hospital-based study, conducted primarily in mid-level countries in East Asia and Latin America, found a lower overall stillbirth rate of 12.5 per 1000 deliveries with a much lower proportion (7.6%) of intrapartum-related stillbirths.(16)

Causes of Stillbirth

Although certain events likely cause stillbirth, identification of the cause at this period of life is complex, and even with placental pathological examinations and autopsies about the cause cannot be identified half of stillbirths. (22, 23) The proportion of stillbirth that is unexplained varies, based, in part, on the classification system used, the amount of information available to determine cause, and the biases of the person conducting the review. (18, 23)

Multiple factors may act directly on the fetus or indirectly on the mother. Especially in many developing country settings, and particularly those with a high proportion of home deliveries, why the fetus died will often be unknowable, and the percentage of stillbirths

without a clearly defined cause will be even higher.(2) Nevertheless, in a general way, the major causes of stillbirth in developing countries can be described (Table 1).

Estimates suggest that infection contributes to nearly half of the stillbirths in developing countries. (24–29) Infection may lead to stillbirth through several pathways. First, through maternal infection resulting in systemic illness, i.e., high maternal fever or respiratory distress, the fetus may die, without the organisms transmitted to the placenta or fetus. Next, the placenta may be directly infected without spread of the organisms to the fetus with reduced blood flow resulting in a stillbirth. (24) Finally, infection of the fetus may damage vital organs resulting in stillbirth or may result in an anomaly that later kills the fetus.

A substantial proportion of the infection-related stillbirths in developing countries occur secondary to fetal infection with bacteria that also cause chorioamnionitis. In developing countries, infections with Gram negative organisms such as *Klebsiella Pneumoneae* or *E Coli* may be the most common of these. (24) Syphilis is prevalent in Sub-Saharan Africa more than 10% of pregnant women are seropositive in some geographic areas. Where this occurs, up to half of all stillbirths are in syphilis seropositive women and estimates suggest that 25% of all stillbirths are attributable to syphilis alone. (29,30)

Almost half of all births worldwide occur in areas with endemic malaria, where there are particularly high rates of stillbirth. (Desai) Although malaria is generally not associated with higher stillbirth rates in multigravidae, women infected for the first time in pregnancy are at higher risk for stillbirth.(31,32) Placental damage is the likely cause for stillbirths associated with maternal malaria. [ADD - Desai]

Many other infections have been associated with stillbirth, but their impact in developing countries is unknown. Lyme disease, caused by the spirochete *B burgdorferi*, occasionally causes stillbirth. Interestingly, at least one report from Tanzania found that *B burgdorferi* seropositivity is more than 30%, but the relationship to stillbirth in Tanzania is unknown. (33) African tick-borne relapsing fever, another spirochetal disease, has also been associated with stillbirth. One study reported a perinatal mortality rate of 30% with maternal infection, and described relapsing fever spirochetes in the placenta.(34) The contribution of this disease to the overall stillbirth rate in Sub-Saharan Africa is unknown. Leptospirosis, still another spirochetal disease, has also been associated with transplacental infection and has been described a potential cause of stillbirth in China. (35) Chagas disease, caused by Trypanosoma cruzi, is widespread in South America and may infect the fetus and placenta, causing fetal death. (36) As with African sleeping sickness, the extent to which maternal infection is linked to stillbirth is still unknown. Despite the many unknowns, in certain developing countries, it appears clear that maternal infection contributes significantly to high stillbirth rates.

Since the proportion of all births complicated by a major anomaly is relatively similar in most populations, in developing countries with high incidences of stillbirths due to the other causes, the proportional role of congenital anomalies is significantly less than other causes. (3) Recent studies have attributed less than 5% of stillbirths to congenital anomalies, (Ngoc, GN, etc) compared to nearly a quarter due to anomalies in developed countries.

Another important cause of stillbirth in developing countries is prolonged labor, which may result from feto-pelvic disproportion from contracted pelvices associated with childhood malnutrition. Although fetuses do not die from the labor itself, fetal death may result from associated asphyxia, trauma and infection that typically accompany prolonged labor. (38) Appropriate cesarean sections typically reduce the impact of these complications. Although it has been estimated that overall cesarean section rates of about 5% are needed to reduce the

morbidity and morality associated with prolonged labor, cesarean section rates lower than 1% are found in many developing countries. (39) A related cause of stillbirth is fetal malposition. When available, these fetuses generally are delivered by cesarean section to prevent the complications of prolonged labor. However, when cesarean sections are not accessible, mortality from these complications is high. Similarly, twin pregnancies are often complicated by malpositions, prolonged labor and high fetal mortality from the same causes.

Finally, an important cause of stillbirth is preeclampsia/eclampsia, which occurs in about 6% of pregnancies world-wide. Preeclampsia/eclampsia decreases blood flow, causing poor fetal growth and hypoxia and often resulting in stillbirth. For example, in a hospital-based study from Pakistan, hypertensive disease including pregnancy-induced hypertension and eclampsia, accounted for 24% of the stillbirths. (14). While currently there are not treatments to reduce the incidence of preeclampsia, with screening and medical management, including early delivery, the stillbirth rates could potentially be reduced. However, where blood pressure and urine protein screening are not routine, and where induction of labor or cesarean sections are unavailable, fetuses frequently die secondary to hypoxia associated with maternal preeclampsia or eclamptic seizures. Another cause of fetal asphyxia and stillbirth is cord accidents. While there are not good data available about the number of stillbirths occurring secondary to asphyxia/hypoxia, approximately 25% of perinatal deaths are attributed to asphyxia. (3, 4, 16, 26) In developed countries because intrapartum stillbirth is reduced with adequate care, it is likely that stillbirths could be reduced significantly with adequate care in developing countries. (8)

Risk Factors for Stillbirth

Risk factors are characteristics associated with, but not obviously causal for stillbirth, such as advanced maternal age. The most common risk factors for stillbirths in developing countries include the lack of a skilled attendant at delivery, low socioeconomic status and poor nutrition, prior stillbirths, and advanced maternal age.

Women who lack skilled care at delivery and who do not have access to emergency obstetrical care are among those at greater risk for stillbirth. (40) In many developing countries, one-third or more of the women in labor are attended by skilled birth attendants and deliver at home. (41) Since complications associated with delivery are one of the main causes of stillbirth, the presence of a skilled birth attendant is often critical. In comparing stillbirth rates to measures of obstetric care, intrapartum stillbirth rates were correlated more closely with obstetric care measures, especially c-section rates, than were antepartum stillbirth rates suggesting that intrapartum stillbirth is more closely related to medical care availability. (5) This relationship was not unexpected, since it is well known that in many developing countries, prolonged and obstructed labor and associated asphyxia, is a major cause of stillbirth. (4) Since preeclampsia/eclampsia is another important cause of stillbirth, timely delivery, and availability of cesarean section, can reduce stillbirth associated with both of these and many other conditions.

Cesarean section is one component of essential obstetric services, which also includes the ability to provide parenteral antibiotics, blood transfusion, oxytocic drugs and anticonvulsants, and manual removal of the placenta and retained products of conception. (42) In developing countries, having a skilled attendant at delivery does not equate to availability of essential obstetric services and especially cesarean section. (43) For example, a skilled attendant may be a nurse without training in the performance of cesarean sections or without necessary equipment with which to perform surgery. Thus, while the presence of a skilled attendant may be a component of essential obstetric services, this measure does not capture the performance of the often life-saving cesarean section, or the use of other life-

saving treatments such as antibiotics or blood transfusion. In general, it has been shown that even among the countries with the least resources, c-section and other resources are disproportionately allocated, so for example the richest quintile may have a 7% c-section rate, while the poorest have <1%. (Stanton)

In most geographic areas, in addition to access to obstetrical care at delivery, various other socio-demographic factors, including rural residence, low socioeconomic status, lack of education, lack of a partner, and poor nutrition have been associated with increased stillbirth rates. (44–48) In addition, advanced maternal age is a stillbirth risk factor in all areas of the world. For example, in one study in Latin America, women >35 years of age were twice as likely (31/1000 vs.16/1000) to have a stillbirth as younger women. Finally, short inter-pregnancy intervals, prior stillbirths and a history of adverse pregnancy outcomes have been associated with increased risk of stillbirth. (22)

Strategies to Reduce Stillbirth

Few developing country trials that have specifically attempted to reduce stillbirth, though many have evaluated perinatal mortality (stillbirths and early neonatal deaths) as outcomes. In a comprehensive review of these strategies, Bhutta et al found that… Specific strategies that have been evaluated to reduce stillbirth in developing countries include reduction of infection and improvement in maternal nutritional status. Trials to reduce infection have had varying levels of success in reducing stillbirth. Malaria prophylaxis with chloroquine in endemic areas has been the primary strategy, but there is uncertainty about its efficacy in comparison with intermittent presumptive treatment. (54) Identification and early treatment of syphilis is another strategy used to reduce stillbirth-related infections.(55) Logistical issues, such as the complexity of tests, maintaining supplies and low follow-up remain challenges to effective screening and treatment in many regions.(56)

Finally, nutritional supplementation has shown inconsistent results in reducing stillbirth. Introduction of various nutritional strategies specifically aimed at reducing a common cause of stillbirth, preeclampsia, including caloric and protein supplementation, vitamin/mineral supplementation, antioxidants, and probably calcium, have generally been ineffective. (57–59) Few nutritional supplementation trials have specifically evaluated stillbirths; however, several caloric supplementation trials in very low-resource settings have significantly improved pregnancy outcomes.(60,61) Thus, while malnutrition is a recognized factor for adverse pregnancy outcomes, further research is needed to identify effective interventions in these settings.

In addition to the strategies that have been tested in developing countries described above, several strategies have successfully reduced stillbirth in developed countries and with successful implementation likely would decrease stillbirths in developing countries. These strategies may have potential to reduce stillbirths, but all require further testing to confirm their effectiveness. First, in addressing the causes of stillbirth in developing countries, reducing intrapartum stillbirth in particular is critical to reducing stillbirth rates. Improved access to quality essential emergency services, in particular to timely and appropriate cesarean section, has been suggested as a strategy to decrease intrapartum stillbirth rates. [REF] For example, countries such as Egypt have shown declines in stillbirth rates, linked to reductions in maternal mortality, primarily attributed to increased deliveries in referral facilities, as well as improved quality of facility-based care. (50)

Although improved access to emergency obstetric care should reduce the number of intrapartum stillbirths, sufficient numbers of skilled birth attendants and resources for facility deliveries are not available in many regions. (41) Therefore, a strategy of training community birth attendants to provide basic care, recognize the need for referral and to

stabilize high risk women prior to referral has been proposed an interim solution. (51) Another strategy to reduce stillbirths has included community outreach to improve outcomes. In a recent trial in Nepal, women in the intervention group participated in informational group meetings to address perinatal problems; although the intervention group had a significant reduction in neonatal mortality, stillbirth rates remained unchanged.(52) In contrast, in Pakistan, where approximately 80% of deliveries are attended only by traditional birth attendants (TBAs), stillbirth rates were significantly reduced (5.0 vs. 7.1%, $p < 0.001$) by training TBAs on antepartum, intrapartum, and postpartum care and referral guidelines for emergency obstetrical care. (53) Finally, a comment has been made on neonatal resuscitation as an effective practice to reduce stillbirth?? An effective referral system for complicated deliveries, in conjunction with training, may be the most promising approach.

Finally, better treatment of medical conditions such as diabetes and various forms of hypertension have resulted in significant reductions in stillbirths in developed countries (22) and it is likely effective treatment of these and other medical causes of stillbirth, similar results will be achieved in developing countries.

Comment

Stillbirth remains one of the most common adverse outcomes of pregnancy, yet is among the least studied. Many stillbirths remain undocumented and historically have not been included among the international health indicators.(REF) Registration of all births and stillbirths, together with evaluation of cause of stillbirths are important initial steps for developing countries. (1) In order to understand stillbirth rates and causes between locations, as well as over time, a standard classification system would be important to documenting the etiology of stillbirth in developing countries. Finally, access to appropriate essential obstetric care and reduction of infection are interventions most likely to significantly reduce global stillbirth rates.

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Table 1

Reported Maternal Risk Factors and Causes for Stillbirth in Developing Countries

Causes/risk factors	Comment
Asphyxia and infection associated with obstructed or prolonged labor	25% of stillbirths in some studies (Lawn)
Syphilis	May represent up to 50% of the stillbirths in some regions (DiMario)
Malaria	In non-endemic area, likely contributing factor either directly or through material anemia, etc. (Desai)
Hypertensive disease/pre-eclampsia	Likely contributing factor, but proportion in developing country not well studied (Goldenberg)
Poor nutritional status	Likely contributing factor, but proportion in developing country not well studied (Goldenberg)

Table 2

Strategies to Reduce Stillbirth in Developing Countries

Strategy	Comment
Antenatal care packages	Generally, has not reduced stillbirth (Villar), though specific strategies (deworming; De Silva or tetanus toxoid immunizations; Rahman) have been shown to reduce stillbirth
Multiple micronutrient or protein supplementation	Caloric supplement (protein/energy) (Ceesay; Kielman, Mora) and multiple micronutrient (Fawzi) have been associated with decreased stillbirth rates in low-resource settings
Vitamin A supplementation	Has not been shown to decrease stillbirth (Christian, Fawzi)
Malaria protection or treatment	Malaria chemoprophylaxis has had mixed results but generally not shown to reduce stillbirths (Shulman; Parise; Greenwood, decrease by 50% NS; Nyirjesy decreased PMR; D'Alessandro)
Syphilis screening and treatment	Treatment has been shown to reduce stillbirth rates to equivalent of non-infected women (Chi, Watson-Jones, Temmerman, Osman)
Treatment of hypertension	Has been effective in developed countries but not evaluated yet in developing countries. (Goldenberg)
Antiobiotics for various indications	Generally has not reduce stillbirth, i.e., in treatment for UTIs (Gichangi) or PPROM (Ovalle-Sallas)
Improve access to emergency obstetrical care	Countries with higher c-section rates generally have lower stillbirth rates, but further research needed to evaluate strategies to improve access to care (Belizan, Goldenberg)
Community birth attendant training	Training of traditional birth attendants has shown mixed results; one community study in Pakistan found significant stillbirth reduction (Jokhio) but further research warranted (Sibley)