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Systematic review

Causes of and factors associated with stillbirth in low- and middle-income countries: a systematic literature review

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Background Annually, 2.6 million stillbirths occur worldwide, 98% in developing countries. It is crucial that we understand causes and contributing factors.

Methods We conducted a systematic review of studies reporting factors associated with and cause(s) of stillbirth in low- and middle-income countries (2000–13). Narrative synthesis to compare similarities and differences between studies with similar outcome categories.

Main results A total of 142 studies with 2.1% from low-income settings were investigated; most report on stillbirths occurring at health facility level. Definition of stillbirth varied; 10.6% of studies (mainly upper middle-income countries) used a cut-off point of ≥22 weeks of gestation and 32.4% (mainly lower income countries) used ≥28 weeks of gestation. Factors reported to be associated with stillbirth include poverty and lack of education, maternal age (>35 or <20 years), parity (1, ≥5), lack of antenatal care, prematurity, low birthweight, and previous stillbirth. The most frequently reported cause of stillbirth was maternal factors (8–50%) including syphilis, positive HIV status with low CD4 count, malaria and diabetes. Congenital anomalies are reported to account for 2.1–33.3% of stillbirths, placental causes (7.4–42%), asphyxia and birth trauma (3.1–25%), umbilical problems (2.9–33.3%), and amniotic and uterine factors (6.5–10.7%). Seven different classification systems were identified but applied in only 22% of studies that could have used a classification system. A high percentage of stillbirths remain 'unclassified' (3.8–57.4%).

Conclusion To build capacity for perinatal death audit, clear guidelines and a suitable classification system to assign cause of death must be developed. Existing classification systems may need to be adapted. Better data and more data are urgently needed.

Keywords Causes of stillbirth, factors associated with stillbirth, low income countries, middle income countries, stillbirth classification.

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Introduction

The World Health Organization (WHO) defines stillbirth as a baby born dead at 28 weeks of gestation or more, with a birthweight of ≥1000 g, or a body length of ≥35 cm.[1] Every year at least 2.6 million stillbirths occur worldwide.[2] The vast majority (98%) of stillbirths occur in low- and middle-income countries, and more than half (55%) of these happen in rural sub-Saharan Africa.[2] Although some developed countries report a stillbirth rate (SBR) of 3 per 1000 births,[3,4] a ten-fold increase is noted in some settings in sub-Saharan Africa and South East Asia with reported stillbirth rates of 30 per 1000 births and over.[5,6]

Every stillbirth is a tragedy and a potential life lost. There are in addition many psycho-social consequences for parents, including anxiety, long-term depression, post-traumatic stress disorder and stigmatisation.[1] Sadly, women who have experienced a stillbirth are more likely to experience this again in subsequent pregnancies than those who have not.[7–11]

Data suggest that most of these deaths could be prevented.[2,4] To do so, it is crucial that we understand the causes of and factors that are associated with stillbirth.[1] However, for many cases of stillbirths the cause of death is currently never established.[3,12,13] Cause of death is very often not recorded accurately or not recorded at all. Training of healthcare providers is required to improve their understanding of the causes of stillbirth and factors associated with stillbirth and their ability to conduct perinatal audit.[14] Available systems for classifying the underlying

cause of stillbirth differ in their approach and even when applied there is a high proportion of 'unclassified stillbirths'.[15,16]

Pattinson et al. in a systematic review of perinatal audit in low- and middle-income countries showed that audit conducted at health facility level by healthcare providers has the potential to improve the quality of care.[17] Meta-analysis of seven before-and-after studies also indicated a reduction in perinatal mortality of 30% (95% confidence interval [95% CI], 21–38%) after introduction of perinatal audit.

We conducted a systematic review of the literature to summarise the available information on identification of causes of, and factors associated with, stillbirth in low- and middle-income countries. In addition, we sought to identify which classification systems are used in these settings.

Methods

Search strategy

We searched electronic databases (MEDLINE, CINAHL Plus, Global Health and LILACS) for studies on stillbirth or disease conditions leading to stillbirth conducted between 2000 and 2013 (inclusive), in low- and middle-income countries. The period of 2000 to 2013 was selected to cover the period when many developing countries became more proactive in addressing the burden of maternal and perinatal mortality and morbidity through implementation of programmes to achieve the Millennium Development Goals numbers 4 and 5.

The following terms were used: 'stillb*' AND (causes OR risk OR audit OR review OR 'perinatal audit' OR 'perinatal review').

Inclusion/exclusion criteria

Studies were included if they assessed at least one of the causes of, or risk factors for, stillbirth (irrespective of the stillbirth definition used) and were conducted in low- or middle-income countries as defined by the World Bank income categorisation, 2012.[18]

We excluded studies that did not contain information on causes of or risk factors for stillbirths; were conducted in high-income countries; were published in languages other than English (and did not have an English abstract); or were general discussion papers or reviews not presenting data on causes of, or factors associated with, stillbirths (Figure 1).

Data extraction

Two reviewers independently screened all titles and abstracts. Differences in opinion were resolved by discussion and consultation with a third researcher (seven papers).

A summary table was developed and agreed by all authors before full review of the articles began. All included studies were summarised (Table S1). Outcomes of interest were extracted into SPSS (version 20, NY, USA) to allow for statistical analysis (descriptive).

Data synthesis

We employed a narrative synthesis method. We distinguished between factors associated with (or risk factors for) and causes of stillbirth. When this was not clear in the publication, we defined a (risk) factor associated with stillbirth as 'a maternal/paternal characteristic associated but without an obvious causal relationship with the stillbirth' and cause was defined as 'any condition with a plausible mechanism likely to lead to the death of the fetus'.[19] Studies were considered as population-based if they were conducted at community level with or without involvement of a health facility for a clear catchment population.

The studies were grouped into three outcome categories: those providing information on cause(s) of stillbirths, those with information on factors associated with stillbirth, and those providing information on both causes and associated factors. Where a classification system had been used this was also recorded. For the purpose of summarising findings in this review we used the ReCoDe classification system which classifies cause(s) of stillbirth according to relevant condition at death and is currently the only classification system specifically developed for stillbirth.[15]

Studies were assessed for quality using the GRADE system,[20] with study design, data source, statistical analysis and content clarity used as priority outcomes. The methodologies and results of studies belonging to the same outcome category were compared to look for similarities and differences. The results were discussed with appropriate emphasis given to studies that were more methodologically robust.

Results

Characteristics of studies included

We identified a total of 142 studies for inclusion (Figure 1); 16 papers could not be retrieved for review (most of which were published in the *Journal of the Medical Association of Thailand*, *Nepal Medical College Journal*, *The West Indian Medical Journal* and *Journal of the Indian Medical Association*). The included studies were conducted in 49 countries across six continents (Figure 2). The majority of studies originate from lower middle-income (87/142) and upper middle-income countries (41/142) with only a minority from low-income countries (3/142).

The majority of included studies were carried out in Asia (64/142) and Africa (49/142), with remaining studies

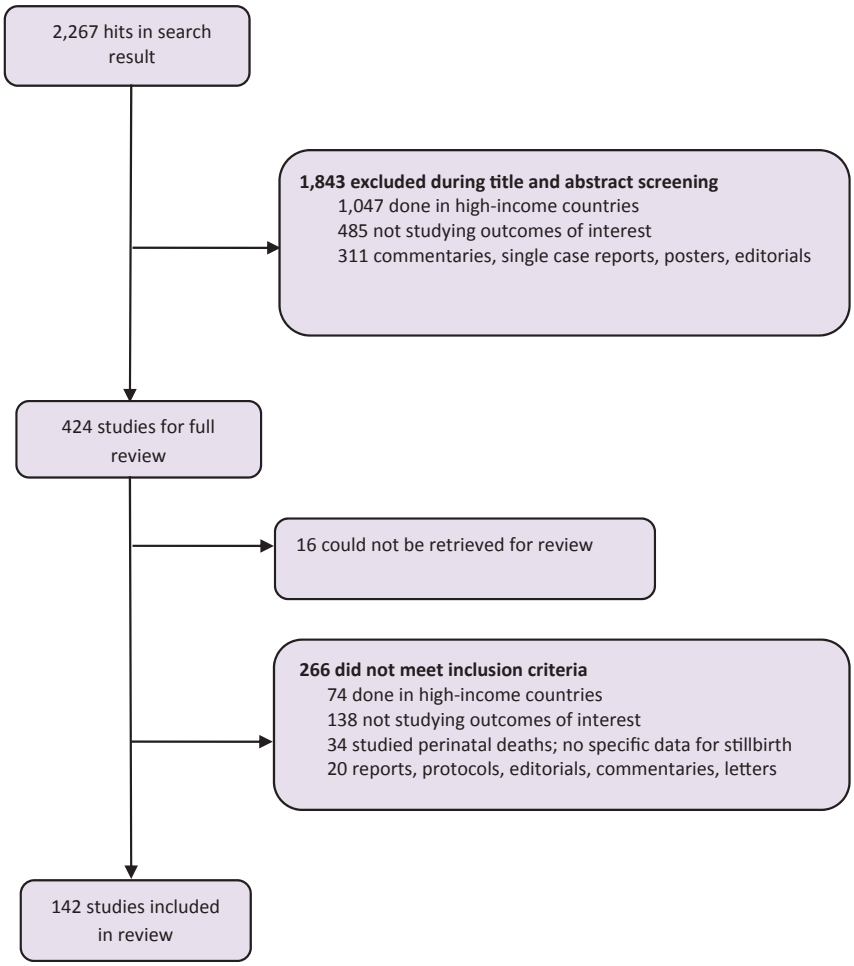

Figure 1. Article selection process.

coming from South America (17/142), Turkey (3/142), Jamaica (1/142) and Papua New Guinea (1/142). Seven studies were each conducted in multiple countries and/or in more than one continent.

Most included studies were descriptive and cross-sectional (76/142) while the remaining studies were designed as case–control studies (29/142), cohort studies (26/142) or clinical trials (6/142). We identified five earlier reviews. Among the reviews, four were systematic reviews[21–24] and one was a traditional, non-systematic review[19] but none of these reviews explored classification systems used in these countries.

There were 76 hospital-based studies and 33 population-based studies. The setting was not described in 33 studies, which were hospital-based for the most part. Studies from Nigeria constituted 9.2% of all papers included in this review, all of which were hospital-based. Similarly, 10.6% of the articles were from India and all but one were hospital-based.[25]

Using the GRADE criteria, of the 142 included studies, the majority (71%) were of very low or low quality; 24% were of moderate quality and 5% were of high quality.

A large proportion (60/142) of the studies reported on factors associated with stillbirth or risk factors only while 32/142 reported on cause(s) only; the remaining 50 studies reported on both risk factors and underlying causes of stillbirth.

Definition of stillbirth

Definition of stillbirth varied between countries and even between studies conducted in the same country. Although most of the studies defining stillbirth used a gestational age of between 20 and 28 weeks as a cut-off point, only 11% (15/142) of the included studies used the standard WHO definition of ≥22 weeks gestation or weight of ≥500 g. Another 32% of studies (46/142) used the WHO definition recommended for international comparison, i.e. ≥28 weeks of gestation or ≥1000 g. A large proportion (29%) of the

Figure 2. Geographical distribution of papers included (size of bubble approximates the number of studies).

studies included in this review did not specify the definition of stillbirth used (Figure 3). Stillbirth definitions represented as 'other definitions' were those that used phrases such as 'a baby delivered dead'.

Studies using the lower gestational age band of between 20 and 22 weeks as a cut-off point for defining stillbirth were from upper middle-income countries such as China, Malaysia, Tunisia and Argentina,[26–32] whereas studies using the cut off of ≥28 weeks tended to be from low-income and lower middle-income settings including Nigeria, India, Bangladesh, Sudan, Ghana, Nepal and Pakistan.[33–39]

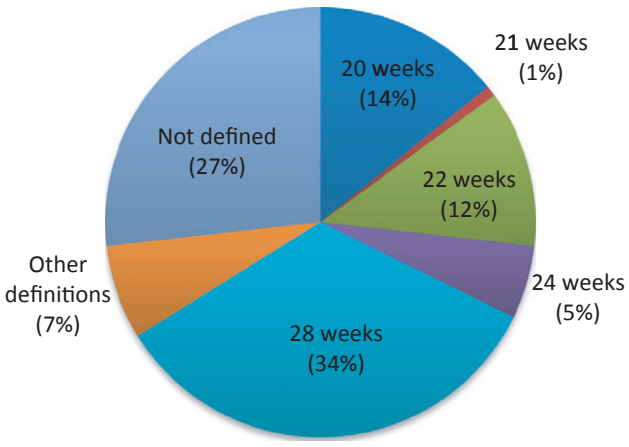

Figure 3. Variations in definition of stillbirth (cut-off point of gestational age) among included studies (n = 142).

Stillbirth rates in developing countries

The reported SBR varied between countries and across country-income categories. The highest SBR were reported in low-income sub-Saharan African and South East Asian countries. Of the 33 population-based studies, 13 did not report on SBR or were focused on participants with conditions known to increase the risk of stillbirth. For the remaining 20 population-based studies, the reported SBR ranged from 6.2 per 1000 births in China[30] to 39.1 per 1000 births in Bangladesh[37] (Table 1).

Factors associated with stillbirth

By far, the most commonly reported factors associated with stillbirth in developing countries were: maternal age; gestational age at birth; parity; lack of or inadequate antenatal care; fetal sex; birthweight; multiple gestation; and maternal morbidity.

Maternal factors

Advanced maternal age (generally described as the age of 35 years and above) was reported as a significant risk factor associated with stillbirth in many developing countries,[5,33,40–45] with an Odds Ratio (OR) of up to 2.31 (95% CI 1.81–2.95) reported from India.[34] For mothers 40 years

Table 1. Mean stillbirth rates reported in population-based studies reporting cause of or risk factors for stillbirth

Country of study	Simple mean stillbirth rate (per 1000 births)	SD	Stillbirth rate range (per 1000 births)	Total births on which reported	Number of studies (reference)
Bangladesh	35.6	2.7923	32.7–39.1	112 691	4 [12,35,39,40]
Pakistan	33.6	–	–	1280	1 [41]
Nepal	33.4	2.8991	31.3–35.4	50 513	2 [27,42]
Ghana	29.1	5.2943	23.0–32.5	61 079	3 [13,33,43]
Zambia	27.0	–	–	1679	1 [44]
Palestine	25.1	–	–	4744	1 [45]
Uganda	19.0	–	–	835	1 [46]
India	13.9	–	–	13 467	1 [23]
Vietnam	12.7	–	–	5259	1 [47]
China	8.1	1.3018	6.2–9.0	2 984 758	4 [26,28,38,48]
Thailand	6.8	–	–	3522	1 [64]

or older in Peru, Gilbert et al. reported an increased risk of stillbirth with adjusted OR of 5.46 (95% CI 1.19–25.13).[43] Conversely, in a study from Nigeria that examined pattern and correlates of stillbirth in a hospital setting, young maternal age (<20 years) was reported to increase the risk of stillbirth (OR 2.50; 95% CI 1.22–5.14) but this was not corrected for other risk factors.[46] There was also a higher proportion of stillbirths reported among teenage mothers when compared with older mothers (5.1% versus 0.9%, respectively) in a hospital setting in India.[47] And in a national survey involving 8481 deliveries in China, mothers 40 years or older (OR 2.98; 95% CI 2.67–3.32) and teenage mothers (OR 2.57; 95% CI 2.29–2.89) were both reported to have an increased risk of stillbirth.[28]

Parity is another frequently reported risk factor in studies from developing countries. In a study that investigated 218 women who had a stillbirth in a hospital in South Africa, Ntuli and Malangu identified primiparity as a risk factor for stillbirth ($P = 0.04$).[29] Similarly, a multicountry study that explored the time when stillbirth occurred during pregnancy found that both primiparity (relative risk [RR] 1.3; 95% CI 1.2–1.5) and parity ≥5 (RR 1.2; 95% CI 1.1–1.3) increased the risk of stillbirth.[5] Both primiparity and parity ≥5 have been associated with stillbirth by several other studies from developing countries, including Palestine,[41] Nigeria,[44] Vietnam,[48] Ghana,[35] Pakistan,[36,49] Nepal[50] and Uganda.[51]

Obstetric factors were frequently described to be associated with stillbirth. Both history of previous stillbirth[8,10,44,50] and mode of delivery[51–53] have been found to be associated with stillbirth. Other factors associated with stillbirth that were reported by various studies in this review include consanguinity[54–56] and smoking, alcohol intake and drug abuse.[57–59]

Fetal factors

In Nepal, Shrestha and Yadav reported prematurity as a major risk factor in their study involving 3588 deliveries.[60] An association between prematurity and stillbirth was reported from Tunisia where an adjusted (for birthweight) OR 6.05 (95% CI 1.85–19.78) was reported among 87 stillbirths studied in a prospective cohort study.[31] Stringer et al., in a study of 2109 stillbirths in Zambia, reported that extremes of birthweight increased the risk for stillbirth (OR for ≤1500 g 56.13, 95% CI 3.48–5.85 and OR for ≥4000 g 2.08, 95% CI 1.54–2.80).[8] Among 91 stillbirths in Brazil, proportionally more were male (52.7%).[61] However, in a large retrospective study from Zimbabwe that explored delivery patterns and outcomes among 17 072 deliveries in a hospital setting, Feresu et al.[62] found no statistically significant difference between the risk of stillbirth in males and females.

Access to care

There were a number of studies reporting on the association between lack of antenatal care and stillbirth. Nouaili et al.[31] found that inadequate antenatal care increased the risk of stillbirth in a Tunisian population with an adjusted OR of 3.50 (95% CI 1.07–11.43). Similar results were reported from Peru (OR 3.39; 95% CI 1.57–7.74),[43] Nigeria (OR 7.23; 95% CI 3.94–13.26),[53] Jamaica (OR 2.0; 95% CI 1.3–3.1)[63] and Vietnam (OR 2.56; 95% CI 1.25–5.23).[64]

Factors related to care setting and place of birth have also been reported to influence stillbirth. A prospective cohort study of 5259 births in Vietnam reported that women who delivered at home were at significantly higher risk of stillbirth than those who delivered in a health facility (OR 6.81; 95% CI 2.40–19.30).[64] Rural residence has also been reported to contribute to the risk of stillbirth in

India (OR 2.05; 95% CI 1.93–2.18),[34] Vietnam (OR 2.42; 95% CI 1.16–5.03)[48] and the Gambia (OR 6.68, 95% CI 3.84–11.62).[65] On the other hand, a community-based prospective cohort study involving 835 deliveries in Uganda has reported a significant increase in risk of stillbirth among urban residents (RR 2.9; 95% CI 1.1–7.7).[51]

Socio-economic factors and education

Low socio-economic status has been reported by several studies as contributing to stillbirth in developing countries. In a systematic review of risk factors for stillbirth in developing countries, Di Mario et al.[21] identified maternal socio-economic disadvantage as one of the factors with a population attributable fraction of higher than 50%. This association has been reported recurrently from other developing countries.[35,48,50,64,66,67] Williams et al. have reported wealth index and caste as significantly associated ($P = 0.001$) with stillbirth in India.[68] Bhatacharyya and Pal also reported this association in India (OR 1.81; 95% CI 1.76–1.90),[34] Graner et al.[64] reported an increased risk of stillbirth among ethnic minorities in Vietnam. In Burkino Faso (from verbal autopsy data) stillbirths were more common among women in a monogamous marriage (61.0%) than in a polygamous marriage (33.6%; $P < 0.01$).[66]

In a hospital-based study in Nigeria, Mutihir and Eka reported a statistically significant association between low maternal education and stillbirth ($P = 0.01$).[38] In a study that explored stillbirth rates in five developing countries involving 60 154 births, lack of formal education was found to increase the relative risk of stillbirths by 1.6 (95% CI 1.4–1.8).[6] A number of other studies have also reported the association between low or poor maternal education and stillbirth including from Ghana (RR 1.4; CI 1.2–1.5) and Brazil (OR 1.6; 95% CI 1.02–2.6).[5,35,41,51,57,68,69]

Three studies reported on environmental pollution as a risk factor for stillbirth.[22,28,64] In a systematic review that included four studies, Pope et al. reported that indoor air pollution was associated with stillbirth (OR 1.51; 95% CI 1.23–1.85).[22]

Causes of stillbirth

For each included study, attributed cause (or causes) and relative percentage contribution to stillbirth were extracted and a summary table was constructed using the ReCoDe framework (Table 2).

Maternal disease

A total of 21 studies identified one or more maternal diseases as the cause of stillbirth. The percentage attribution ranged from 8 to 50% of stillbirths. Maternal conditions as causes of stillbirth such as diabetes, HIV, syphilis and hypertensive disorders were the most commonly reported.[19,70]

Underlying maternal morbidity is reported as increasing the risk of stillbirth in a number of developing country settings. In Ghana, malaria was reported to increase the risk of stillbirth with odds ratio of 1.9 (95% CI 1.2–9.3)[10] and HIV,[7,71,72] syphilis,[73–76] anaemia[77] and toxoplasmosis[78] have also been associated with stillbirth in developing countries.

In a large cross-sectional study involving 120 998 deliveries that assessed the trend of stillbirth in Thailand over a decade, Tannirandorn and Jatuparisuth reported the increasing importance of causes of stillbirth related to the mother's condition, particularly diabetes and haemoglobinopathies.[79] In another study of similar size in Zambia, Stringer et al. reported a statistically significant association between hypertension and diabetes and macerated stillbirth (OR 1.40 [1.11–1.75] and 3.86 [1.27–11.70], respectively) but found no association with fresh stillbirth.[8]

A clinical trial among 1229 HIV-infected mothers found an increased risk of stillbirth among mothers with a higher plasma viral load and who were symptomatic (adjusted OR 3.19; 95% CI 1.46–6.97).[72] Similar results were obtained in

Table 2. Reported causes of stillbirth in developing countries arranged based on frequency of reporting

Attributed cause of stillbirth	% cause range	No. of studies reporting causes	Total no. of stillbirths reported on	No. of stillbirths per study
Mother's disease: e.g. diabetes, HIV, syphilis	8–50	21	6392	12–1748
Fetal: e.g. congenital anomalies, infections	2.1–33.3	16	3040	12–640
Placental: e.g. placenta praevia, placental abruption	7.5–42	12	3024	12–640
Intrapartum: e.g. asphyxia, birth trauma	3.1–25	6	1094	24–735
Umbilical: e.g. prolapse, loop, knot	2.9–12	6	660	17–266
Trauma: e.g. iatrogenic	5–28	3	901	32–735
Amniotic: e.g. chorioamnionitis, oligohydramnios	6.5	1	169	169
Uterine: e.g. rupture, anomalies	10.7	1	169	169
Unclassified/unknown/unexplained	3.8–57.4	16	5313	12–1748

Categories of causes adapted from ReCoDe classification.[13]

a separate trial among HIV-positive women in Tanzania where CD3 count >1179 cells/ml was reported to increase the relative risk of stillbirth by 2.15 (95% CI 1.16–4.01).[7] Conversely, in a multinational study involving 2434 deliveries among predominantly HIV-positive women, Chi et al. found no association between HIV-infection and stillbirth (Adjusted OR 1.11; 95% CI 0.38–3.26). They, however, reported that decreasing CD4 count was inversely associated with stillbirth risk ($P = 0.009$).[71]

Positive syphilis serology (rapid plasma reagin titre of ≥1:16) was associated with stillbirth in a case–control study of 138 stillbirths in Guinea-Bissau (adjusted OR 8.29; 95% CI 3.14–21.89).[73] Temmerman et al.[75] studied 296 women with confirmed syphilis in Kenya and reported an increased risk of stillbirths (OR 3.34; $P = 0.028$). In Tanzania, a retrospective cohort study of 18 stillbirths found that the risk of stillbirths among women with a positive rapid plasma reagin test was significantly higher than those with a negative result (RR = 18.1; $P < 0.01$).[76]

Congenital anomalies

Congenital anomalies are reported to account for 2.1–33.3% of stillbirths.[80,81] Renal, pulmonary and cord abnormalities accounted for four out of 12 (33%) stillbirths in a study that examined postmortem reports in Malaysia.[81] In a community-based study of all perinatal deaths in four cohorts in selected districts of Thailand using verbal autopsy, Mosuwan et al. reported that congenital anomalies including anencephaly, diaphragmatic hernia and thanatophoric dysplasia accounted for four out of 24 stillbirths.[82] In Brazil, Andrade et al. retrospectively studied all fetal deaths in a hospital setting by examining records and conducting verbal autopsy. They reported a strong association between fetal malformation and stillbirth (OR 7.5, 95% CI 3.2–17.4), and this accounted for 10.3% of the 25 stillbirths.[69] Another study in Brazil that reviewed autopsy records of all stillbirths ($n = 111$) in a hospital reported that 26% were caused by congenital anomalies.[83] In India, two separate studies found that fetal anomalies accounted for 12% and 23% of 570 and 26 stillbirths, respectively.[84,85] Similar results were reported from Nepal where 18% of 17 stillbirths were due to congenital anomalies in a study that examined medical records,[86] and in Turkey where a cross-sectional examination of hospital records found that congenital anomalies accounted for 19% of 32 stillbirths.[58]

Placental conditions

Placental causes, particularly placental abruption, are recognised in many studies as a major cause of stillbirth, with a percentage attribution of between 7.5 and 42%.[81,87]

A study involving 495 stillbirths in multiple West African countries, strongly associated vaginal bleeding in late pregnancy or intrapartum bleeding with stillbirths (OR 15.1; 95% CI 11.1–22.1).[88] In another study of 4744 deliveries, Kalter et al.[89] reported uteroplacental insufficiency as one of the top three causes of stillbirth, accounting for 31% of all macerated stillbirths. Antepartum haemorrhage was responsible for one-third of 309 stillbirths in rural Ghana[90] and one-third of 140 stillbirths in Pakistan.[49]

In another study that conducted verbal autopsies in four countries, antepartum haemorrhage was estimated to have accounted for 10% of 134 stillbirths.[42] A related study in India reported that 16% of 570 stillbirths were due to antepartum haemorrhage.[85] Placental causes have also been reported as important in Nigeria, accounting for 20.1% of 266 stillbirths.[92] While in South Africa placental causes were reported to account for 24% of 218 stillbirths in a tertiary hospital.[29]

Intrapartum causes and trauma

Between 3.1 and 25% of stillbirths were due to intrapartum causes (including asphyxia) and trauma.[34,92] A prospective cohort study of antenatal attendees in Tanzania found that, of 60 stillbirths, 15 (25%) were due to asphyxia-related causes,[92] while a study from four districts in Thailand found that intrauterine asphyxia accounted for 21% (5/24) of stillbirths.[82] Similarly, Bhattacharya and Pal reported that while intrauterine asphyxia was the cause of 16.7% of 177 stillbirths, trauma accounted for 3%.[34] In a retrospective study, misuse of oxytocin was thought to have accounted for 28% of 735 stillbirths in a teaching hospital in Bangladesh.[93] A hospital-based cross-sectional study in China studied 58 'fetal losses' among 3498 women who had amniocentesis planned or performed between 15 and 22 weeks of gestation and reported an association between mid-trimester amniocentesis and stillbirth (OR 1.97, 95% CI 1.15–3.36).[94]

Umbilical causes

Umbilical cord accidents have been strongly associated with stillbirth (OR 29.63, 95% CI 14.23–61.71).[46] Overall umbilical causes were reported to be responsible for 2.9–12% of stillbirths.[70,91]

In Zambia, umbilical causes accounted for 12% of 50 stillbirths in a cross-sectional study.[71] Two separate studies from Nigeria have reported lower percentages (7% and 2.9%) among 158 and 266 stillbirths, respectively,[38,91] while a similar result (6%) was obtained in a multinational study involving 134 stillbirths.[42]

Amniotic and uterine causes

Amniotic and uterine causes were the least frequently reported causes of stillbirth in studies from developing countries, accounting for 6.5% and 10.7%, respectively.[44]

In a prospective cohort study of 1369 Pakistani women attending antenatal care, Jehan et al.[95] have reported that

chorioamnionitis significantly increased the risk of stillbirth (RR 4.6; 95% CI 2.1–9.8). A systematic review that measured the impact of risk factors on stillbirth has reported a population attributable risk of higher than 50% for chorioamnionitis.[21]

Uterine rupture accounted for 26.7% of deaths in a study of 263 stillbirths among 728 women with severe acute maternal morbidity in Nigeria.[52] A second study from Nigeria involving 169 stillbirths among all women (2326) found 10.7% of stillbirths to be due to ruptured uterus.[44]

Causes unknown

Many studies reported a large proportion of stillbirths as unclassifiable or as cause 'unknown' (3.8–57.4%).[13,96]

Nearly half of all stillbirths were reported as cause 'unknown' in studies from Bangladesh (49%)[12] and Nepal (47%).[86] In Nigeria, Kuti et al.[91] reported 38.8% of 266 stillbirths as unexplained, while in Mumbai (India) 18% of 105 stillbirths identified in a prospective study involving 13 467 births were classified as cause unknown.[25] In rural Ghana, 57.4% of antepartum deaths and 31.5% of intra partum deaths were reported as 'unexplained'.[13] In a multi country study, 12% of 134 stillbirths were reported with cause unknown.[97]

Figure 4 illustrates that the distribution and range of the percentage of stillbirths with attributable cause described is generally fairly evenly distributed within the given range except for intrapartum and trauma.

Classification systems for stillbirth used in developing countries

Currently, a variety of classification systems are used across geographical regions (Table 3). Out of 59 studies that reported on more than one cause of stillbirths, 19 (32%) did not use any classification system at all while over half (34/59) used only terms such as 'fresh/macerated' and 'antepartum/intrapartum' to classify the time of death. Only 12 studies used classification systems such as the Extended Wigglesworth or Aberdeen Classification System (six countries: Bangladesh, Brazil, Nepal, Pakistan, Tanzania and Vietnam) to help decide cause of death. One study from China classified stillbirth according to the recommendations of their National Institute of Child Health and Human Development.

A total of 33 studies reported on percentage of stillbirths that were 'fresh' or 'macerated' (31/33 used only this categorisation). The mean percentage of 'fresh' stillbirths among the 33 studies was 52.6%. While hospital-based studies (n = 23) reported a mean percentage of 50.6%, population-based studies (n = 10) reported 58.5% as the mean percentage for 'fresh' stillbirths.

At least five studies reported a 'fresh' stillbirth proportion of more than 70%.[5,10,70,87,98] The highest was from a study involving 25 982 deliveries in Nepal where Manandhar et al.[99] reported 84% of stillbirths as 'fresh', and a multinational study of 1472 stillbirths found the presence of maceration in only 17.2%.[6] On the other hand, Andarde et al.[69] reported only 4.3% of stillbirths as intrapartum among 116 deaths in a hospital in Brazil.

Discussion

We conducted a systematic review to identify the factors reported to be associated with stillbirths as well as the documented underlying cause(s) of stillbirth in low- and middle-income countries. In addition, we identified which classification systems are currently used in these countries. Our findings highlight the need to improve standardisation

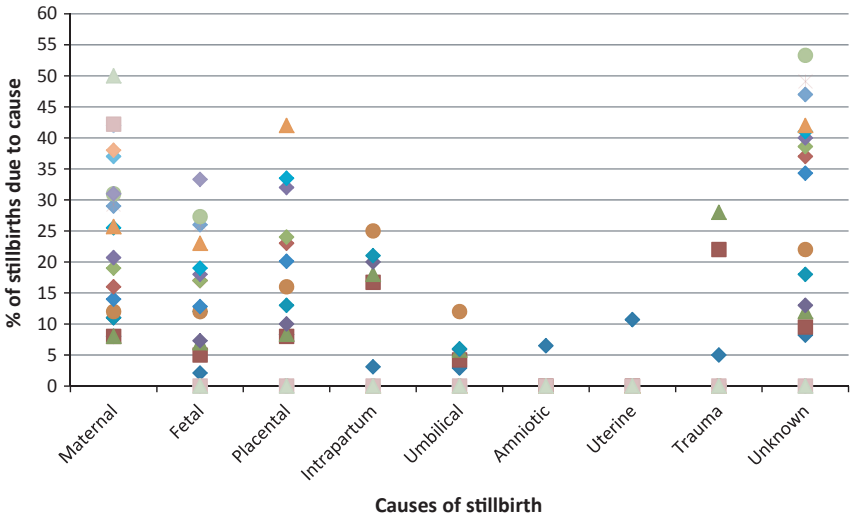

Figure 4. Studies attributing causes of stillbirth.

Table 3. Classification systems used in studies from low- and middle-income countries to attribute cause of stillbirth

Classification system used	Africa	Asia	South America	Multiple continents	Total number of studies
'Fresh/ Macerated'	21	8	1	1	30
Not documented	2	11	2	1	17
Wigglesworth	1	3	0	0	4
Aberdeen	0	2	0	1	3
ICD-10	0	0	2	0	2
'Maternal/ Placental/ Fetal'	0	0	1	0	1
Nordic–Baltic	1	0	0	0	1
PSANZ-CPG/ PDC	0	1	0	0	1
NICE and CHERG	0	1	0	0	1
Total	25	26	6	3	60

ICD, International Classification of Diseases, PSANZ-CPG/PDC, Perinatal Society of Australia and New Zealand Clinical Practice Guide/Perinatal Death Classification, NICE, Neonatal and Intrauterine Death Classification according to Etiology, CHERG, Child Health Epidemiology Reference Group.

across countries with regard to the definition of stillbirth, identification of factors associated with stillbirth as well as attribution of cause.

There were only a few papers from low-income countries (3/142), indicating that fewer studies are conducted in these countries. However, it might also be explained by the fact that there are now fewer low-income countries in the world than there are middle-income (although many of the middle-income countries are in the lower-middle income category). In the reference year (2012), there were only seven countries that fell under the World Bank criteria for low-income country category (i.e. GNI per capita of $1035 or less). Studies from Taiwan and Hong Kong were particularly difficult to place since their economies were clearly in the high-income category but they are officially governed by China, an upper-middle country.

Stillbirth rates are high in the included studies, with many reporting rates of over 30 per 1000 births. Most of the identified studies on stillbirths from developing country settings are currently hospital-based (76/109 in this study) and by definition this makes it difficult to provide meaningful population level rates. It is likely that the risk of stillbirth is higher with a community-based or home birth (that occurs without a skilled birth attendant) and therefore many more stillbirths may occur at this level. Data on cause of stillbirth are collected relatively infrequently at this level.[31] Although at health facility level most maternity registers record information on condition at birth (alive, stillborn), stillbirth is currently not recognised in the Global Burden of Disease; it is neither counted as missed lives in disability-adjusted life-years nor fully identified as an individual death by the International Classification of Diseases.[1] Furthermore, it is reported that stillbirths are not counted in country data in 90 countries worldwide.[1] This lack of recognition and paucity of data on stillbirth has continued to make it difficult to assess the true rates of stillbirth in many developing country settings.[3]

We note that the definition of stillbirth varies between countries and sometimes between studies from the same country. The choice of a definition will determine the number of deaths counted as stillbirths. Upper middle-income countries more often use a lower gestational age cut-off point and so 'count' more babies who are not born with signs of life, while low-income and lower middle-income countries tend to use a higher gestational age cut-off point. This may be related to technological advancement and the ability to provide care for babies born at a certain gestational age to increase the chance of survival. Adopting a common definition of stillbirth among countries (such as provided by the WHO) will allow for more uniform reporting with comparability across countries and would provide a clearer understanding of the extent of the problem nationally and internationally.

There were conflicting views with regard to what is considered a 'risk factor' for stillbirth and what is considered a 'cause' of stillbirth, and most authors used the two terminologies interchangeably. Whereas many factors reported to be associated with stillbirth are related largely to the pregnant woman and her community, reported underlying causes are mostly related to clinical conditions. Some papers have associated prematurity with stillbirth, and it could be argued that as the baby has to be alive to suffer the consequences of prematurity, the condition may not be associated with stillbirth. Many of the reported clinical conditions could be diagnosed and managed even at lower levels of care or could have been prevented with better availability and quality of care during pregnancy or birth. Therefore, for the healthcare provider, a distinction between the two is important to identify what can be done to improve care at the health facility level.

Previous systematic reviews have found that the most common factors associated with stillbirths in developing countries were the lack of adequate antenatal care, lack of a skilled attendant at delivery, low socio-economic status, poor nutrition, previous stillbirths and advanced maternal age.[3,21] The most commonly recognised and previously reported causes of stillbirth from developing countries are hypertensive disorders in pregnancy as well as asphyxia,

trauma and infection that typically accompany prolonged labour.[3,19] In this systematic review we identify a wider spectrum of both factors reported to be associated with stillbirth and attributed cause of stillbirth in low- and middle-income settings.

Maternal disease conditions such as syphilis, hypertensive disorders in pregnancy, diabetes, and HIV (symptomatic or with low CD4 counts) were the most frequently studied factors associated with stillbirth in this review. Among stillbirths with known cause of death in high-income countries, placental causes represent the most frequent cause of death.[100] This may be explained by the better diagnostic capabilities. The lack of diagnostic equipment in developing countries may explain why intrauterine growth restriction has not featured in the findings of this review. The effect of maternal diseases on stillbirth and indeed many of the other major risk factors and causes of stillbirth in developing countries could be reduced by better antenatal screening and treatment for underlying or comorbidity[5,28,60] and by improving the uptake and quality of intrapartum care for women.[2,28]

Congenital anomalies which were thought to be one of the most common causes of stillbirth in developed countries[100] are increasingly reported as cause of stillbirth in studies from developing countries. This may be because a large proportion of the studies in this review (41/142) were conducted in upper middle-income countries with relatively better diagnostic and treatment capabilities. These findings may not be generalisable to lower-income settings. While the most frequent congenital causes of stillbirth in high-income countries are cardiovascular and chromosomal,[100] this more detailed information is not available for most developing country settings.

Even for studies using one of the currently available classification systems for attribution of cause of stillbirth, up to 57.4% of stillbirths remain unclassified. In contrast, unknown causes of stillbirth account for 30% of stillbirths in high-income countries, although this could be as low as 5% with full assessment.[100] A clear understanding of the causes of stillbirth is vital to the success of programmes aimed at reducing the burden of stillbirth. This will require a more intensive programme of capacity building of healthcare providers as well as policy makers to understand and recognise the causes of stillbirth and to evaluate cases of stillbirth using audit to identify where change in practice can be and need to be made.

The use of terms such as 'fresh' or 'macerated' stillbirth is now relatively common with about half of relevant studies using this classification. However, this is too often the only categorisation used. If used correctly ('no shame no blame'), this simple classification may help in defining an approximate time of death but may not be helpful when trying to establish a more precise cause of death or other factors including provision of sub-standard care during the antenatal period. The high proportion of fresh stillbirths observed in many of the studies, however, does indicate that the quality of care during the time immediately preceding birth and at the time of birth at health facility level needs to be improved.

Different countries have adopted different ways of classifying perinatal mortality including stillbirth. Currently there are over 35 classification systems for stillbirth and/or perinatal mortality, none of which has been clearly agreed and adopted globally. These classification systems use different approaches resulting in poor comparability between studies and settings,[2,16] and they consistently report about two-thirds of stillbirths as unexplained.[15] Some of the widely known classification systems, including the Extended Wigglesworth and Amended Aberdeen, are considered unsuitable for classification of stillbirths.[16]

The high number of classification systems available, each focusing on one or more areas of fetal (e.g. Wigglesworth), maternal (e.g. Aberdeen) or placental causes, makes it even more difficult for developing countries to adapt a system that will work in all or at least most countries. However, when six of the popular classification systems (Amended Aberdeen, Extended Wigglesworth, PSANZ-PDC, ReCoDe, Tulip and CODAC) were evaluated on their ability to classify stillbirths, ease of use, inter-observer agreement and ability to retain information, Flenady et al. reported that CODAC performed best with PSANZ-PDC and ReCoDe performing well.[16] ReCoDe is currently the only classification system specifically developed for classification of cause of stillbirth and we have found this relatively easy to apply across the studies included in this systematic review. However, there is still a real need to develop and agree upon a simple classification system that can be used at health facility level in low- and middle-income countries.

Despite all efforts, we were not able to retrieve all the papers in our search results. This indicates that studies conducted on stillbirth are not always reaching mainstream sources of literature, particularly for smaller in-country studies, and highlights the need to improve effort to prioritise the importance of stillbirth as a public health issue. The results of this review may have been affected by the quality of the papers and publications as well as selection biases since currently a comparatively large number of studies pertain to causes of stillbirth related to maternal factors rather than all possible factors associated with or known to cause stillbirth.

Currently, most developing countries do not use any of the popularly known classification systems to classify stillbirth. However, findings of this review suggest that many recognised factors associated with stillbirth are indicative of a level of quality of care that can be improved. It is important to build capacity of healthcare providers to carry out

perinatal death audit using clear guidelines and a suitable classification system that enables causes and risk factors to be identified.

Further research should be focused on standardisation and reporting of stillbirths, including the development of a simple classification system.

Disclosure of interests

All authors declare no conflict of interest.

Contribution to authorship

MA took part in designing the study, conducted title and abstract screening, took part in the full review of articles, extracted and analysed the data and wrote the initial draft of the paper. RU contributed to analysis and writing of the paper. MM independently screened titles and abstracts, reviewed the summary table and contributed to the final draft of the paper. BU took part in the title and abstract screening, reviewed the summary table and contributed to the initial and final drafts of the paper. SA took part in designing the study, reviewed the summary table and the final draft of the article. NVDB conceived the idea and took part in designing the study, oversaw its conduct and analysis and contributed to the initial and final drafts of the paper.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary table for systematic review on causes of and risk factors for stillbirth in developing countries. ■

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