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Preventable stillbirths in India and Pakistan: a prospective, observational study

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Objective Stillbirths occur 10–20 times more frequently in low-income settings compared with high-income settings. We created a methodology to define the proportion of stillbirths that are potentially preventable in low-income settings and applied it to stillbirths in sites in India and Pakistan.

Design Prospective observational study.

Setting Three maternity hospitals in Davangere, India and a large public hospital in Karachi, Pakistan.

Population All cases of stillbirth at ≥20 weeks of gestation occurring from July 2018 to February 2020 were screened for participation; 872 stillbirths were included in this analysis.

Methods We prospectively defined the conditions and gestational ages that defined the stillbirth cases considered potentially preventable. Informed consent was sought from the parent(s) once the stillbirth was identified, either before or soon after delivery. All information available, including obstetric and medical history, clinical course, fetal heart sounds on admission, the presence of maceration as well as examination of the stillbirth after delivery, histology, and polymerase chain reaction for infectious pathogens of the placenta and various fetal tissues, was used to assess whether a stillbirth was potentially preventable.

Main outcome measures Whether a stillbirth was determined to be potentially preventable and the criteria for assignment to those categories.

Results Of 984 enrolled, 872 stillbirths at ≥20 weeks of gestation met the inclusion criteria and were included; of these, 55.5% were deemed to be potentially preventable. Of the 649 stillbirths at ≥28 weeks of gestation and ≥1000 g birthweight, 73.5% were considered potentially preventable. The most common conditions associated with a potentially preventable stillbirth at ≥28 weeks of gestation and ≥1000 g birthweight were small for gestational age (SGA) (52.8%), maternal hypertension (50.2%), antepartum haemorrhage (31.4%) and death that occurred after hospital admission (15.7%).

Conclusions Most stillbirths in these sites were deemed preventable and were often associated with maternal hypertension, antepartum haemorrhage, SGA and intrapartum demise.

Keywords Antepartum haemorrhage, hypertension, preventability, small for gestational age, stillbirth.

Tweetable abstract Most stillbirths are preventable by better care for women with hypertension, growth restriction and antepartum haemorrhage.

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Introduction

Worldwide, it is estimated that each year, of the 140 million pregnancies reaching 20 weeks of gestation or more, about 20–30 per 1000 result in a stillbirth.[1–4] Stillbirths are variably defined by a lower gestational age boundary of 20 weeks in some high-income countries (HIC) to 28 weeks in many low- and middle-income countries (LMIC). The exact numbers and rates of stillbirths occurring at <28 weeks of gestation are unclear. In HIC, stillbirths at ≥28 weeks occur in fewer than six per 1000 births, with ≥28-week stillbirth rates reported as low as two to three per 1000 births in some countries. Of the estimated 2.6 million stillbirths at ≥28 weeks of gestation worldwide, 98% occur in LMIC. In many LMIC, even stillbirths at ≥28 weeks of gestation are unevenly counted, but rates of

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30–40 per 1000 births are commonly reported. In several countries, stillbirth rates at ≥28 weeks of gestation approach 50 per 1000 births. Given the 10- to 20-fold discrepancy in stillbirth rates between HIC and LMIC, it seems likely that many or most of the stillbirths in LMIC are potentially preventable.[1–5]

In a literature review of stillbirths in LMIC, most occurred secondary to fetal asphyxia, and were associated with conditions such as pre-eclampsia/eclampsia, antepartum haemorrhage (including placental abruption and praevia), growth restriction, placental infarcts, fibrosis and necrosis, as well as prolonged/obstructed labour, uterine rupture and umbilical cord accidents.[6] In many cases, we postulated that the stillbirth could have been prevented with identification and treatment of the maternal condition, by screening for a fetal heart rate abnormality or small-for-gestational age (SGA) fetus, and timely operative vaginal or caesarean delivery for fetuses at risk.

Stillbirths occurring in HIC settings with emergency obstetric care technologies and a well-functioning newborn intensive care unit (NICU) are often prevented by delivery at 24 weeks of gestation or later if the fetus is at high risk of demise. Most newborns delivered at 24–27 weeks of gestation in these settings survive. In many LMIC settings, even with NICU care, most newborns delivered before 28 weeks of gestation or at a birthweight <1000 g do not survive.[7]

Preventable stillbirths have generally been defined as those that may be prevented with existing, evidence-based interventions. Several different methodologies have described preventable stillbirths; however, most have addressed HIC,[8] where only 1% of stillbirths occur, or have modelled reductions in stillbirths in LMIC with select interventions.[9–12] We discussed stillbirth preventability with obstetricians, paediatricians and public health officials in several LMIC settings, including in Pakistan and India. Many clinicians focused on the gestational age or the birthweight – factors related to survival of live births – as critical to determine preventability.[13] Based on available data and these discussions, we sought to prospectively define a methodology to evaluate stillbirth preventability in LMIC and apply that methodology to nearly 900 stillbirths that occurred during the PURPOSe Cause of Death study in India and Pakistan.[14]

Methods

Study data were collected as part of PURPOSe, a prospective study conducted from July 2018 to February 2020 in sites in Davangere, India and Karachi, Pakistan to assess the cause of death in stillbirths and preterm neonates delivered in hospital settings.[14] This analysis was restricted to the stillbirths with the objective to determine which stillbirths could have been prevented.

Stillbirths were defined as any fetus born at ≥20 weeks of gestation with no signs of life including no cardiac activity, respirations or movement. Gestational age assessment used a modified American College of Obstetrics and Gynecology algorithm,[15] based on information available at delivery including last menstrual period, ultrasound examination and postnatal physical examination. Because ultrasound use was rare, the gestational age was usually based on the date of the last menstrual period. The preventability analysis was restricted to singleton infants. SGA was defined as birthweight less than the tenth centile of Intergrowth-21st weight for gestational age.[16]

For the PURPOSe study, the sample size for each site was set at a minimum of 350 stillbirths; the methods are described elsewhere.[14] Briefly, staff first identified women with a potential stillbirth before or immediately following delivery. Eligibility included a stillbirth at ≥20 weeks of gestation or, if gestational age was unavailable, ≥500 g birth weight, and the mother of an age and available to provide consent. After consent, trained study staff then collected maternal demographic, obstetric and medical information. Staff also performed an external examination of the fetus and placenta immediately after birth using standardised procedures. Samples of the placenta were collected for histological examination. Polymerase chain reaction (PCR) was used to test for a wide variety of organisms in the placental tissues, membranes and umbilical cord as well as in cord blood. Altogether, we tested for more than 75 pathogens including viruses, bacteria and fungi using Taqman Array Cards (Applied Biosystems, Waltham, MA, USA).[17,18] Photographs of the stillborn fetuses were obtained. Additional consent was also requested to perform minimally invasive tissue sampling, including collect heart blood for PCR and six fetal tissue samples for histology and PCR.[18] A complete diagnostic autopsy was conducted with consent in the Indian site. For each case, all information was collated, and a cause of death was determined by an expert panel.[13,14]

During the panel cause of death reviews, the panel was asked whether the stillbirth was preventable, in their opinion. We recorded those responses separately from the analysis using clinical conditions that are the primary focus of this paper. However, those discussions formed much of the basis for the preventability criteria.

Definition of non-preventability and potential preventability

We prospectively defined the criteria for designating a stillbirth as non-preventable in consultation with panelists, experts and based on the literature review. We then analysed the stillbirth cases for presence of the conditions that met the criteria for the stillbirth being potentially preventable. As the review progressed, in a few instances we

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altered the criteria to make the assignment more logical. One subject matter expert (RLG) reviewed all cases to ensure the criteria were met. Following completion of the individual case reviews, the analyses were also run using a hierarchal model to ensure consistency of coding. We used the terminology 'potentially preventable', because the future outcome of any individual pregnancy is difficult to predict with certainty. We also realise that while we prospectively defined the conditions influencing potential preventability, other categorisations could be adopted. Briefly, stillbirths associated with conditions that could have been identified before delivery and prevented with available interventions were considered potentially preventable.

Non-preventability

All stillbirths with a major congenital anomaly and those with a non-diagnosable or non-treatable congenital infection were defined as non-preventable, regardless of gestational age at delivery (Table 1A). To define a lethal congenital anomaly, all examinations of the fetus including photographs after delivery, external examination, minimally invasive tissue sampling and autopsy were considered.

Table 1. Criteria for preventability

A. Stillbirths not considered potentially preventable at any time or place.
   1. Stillbirth at 20 weeks to <28 weeks of gestation and/or birthweight <1000 g except with a condition considered always potentially preventable. (See B below)
   2. Stillbirths probably caused by a lethal structural or chromosomal anomaly
   3. Stillbirths probably caused by a fetal infection that was not generally preventable or was not able to be diagnosed before the fetal death
   4. Stillbirths with no obvious symptoms or findings to alert the clinician about potential demise

B. Stillbirths considered potentially preventable in high- or low-resource settings at any gestational age >20 weeks of gestation, assuming no lethal anomaly or infection.
   1. Stillbirths probably caused by a vaccine-preventable infection
   2. Stillbirths probably caused by maternal syphilis
   3. Stillbirths probably caused by maternal malaria
   4. Maternal haemoglobin <7 g/dl in the absence of maternal haemorrhage

C. Stillbirths considered potentially preventable in low-resource settings at ≥28 weeks of gestation and/or birthweight ≥1000 g if gestational age is unknown.
   1. Any stillbirth ≥28 weeks of gestation or birthweight ≥1000 g except those with a condition not considered preventable anywhere (Section A)
   2. Stillbirths probably caused by a vaccine-preventable infection
   3. Stillbirths probably caused by maternal syphilis
   4. Stillbirths probably caused by maternal malaria
   5. Stillbirths probably caused by placental malfunction as evidenced by fetal growth restriction
   6. Stillbirths probably caused by pre-eclampsia/eclampsia
   7. Stillbirths probably caused by a placental abruption or placenta praevia
   8. Stillbirths probably caused by a treatable maternal medical disease such as diabetes
   9. Stillbirths probably caused by post-dates (≥41 weeks)
   10. Stillbirths probably caused by a diagnosable/treatable maternal infection
   11. Stillbirths probably caused by an umbilical cord accident
   12. Stillbirths admitted with a heartbeat who died before delivery

D. Stillbirths considered potentially preventable in high-resource settings at 24–27 weeks of gestation and/or birthweight 500–1000 g
   1. Any stillbirth ≥24 weeks of gestation and/or birthweight ≥1000 g except those with a condition not considered preventable anywhere (Section A)
   2. Stillbirths probably caused by a vaccine-preventable infection
   3. Stillbirths probably caused by maternal syphilis
   4. Stillbirths probably caused by maternal malaria
   5. Stillbirths probably caused by placental malfunction as evidenced by fetal growth restriction
   6. Stillbirths probably caused by pre-eclampsia/eclampsia
   7. Stillbirths probably caused by a placental abruption or placenta praevia
   8. Stillbirths probably caused by a treatable maternal medical disease such as diabetes
   9. Stillbirths probably caused by post-dates (≥41 weeks of gestation)
   10. Stillbirths probably caused by a diagnosable/treatable maternal infection
   11. Stillbirths probably caused by an umbilical cord accident
   12. Stillbirths admitted with a heartbeat who died before delivery

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If there was evidence of a lethal fetal anomaly, or the fetus had clinical signs of a trisomy, we classified the stillbirth as non-preventable.

With the exceptions of stillbirths associated with vaccine-preventable infections, maternal syphilis, malaria and a maternal haemoglobin <7 g/dl, all fetal deaths occurring at 20–23 weeks of gestation and 24–27 weeks of gestation and/or birthweight of <1000 g were also considered non-preventable. We made the decision regarding fetuses at 24–27 weeks of gestation because, even if delivered alive, these fetuses generally do not survive in LMIC. Several conditions that might be preventable in HIC were also considered to be non-preventable, such as red blood cell antigen incompatibility, even though this is potentially preventable with Rhesus D immunoglobulin, early delivery or intrauterine transfusion, which are available in HIC but usually not in LMIC. For this study, stillbirths in India and Pakistan associated with these conditions were considered not preventable.

Post-delivery information was often used to determine preventability. For example, even if anencephaly was not diagnosed before delivery, the stillbirth could not have been prevented. Similarly, if after delivery, the fetus was discovered to have a lethal infection but without signs of infection before delivery, the stillbirth was considered non-preventable.

One of our most difficult challenges involved cases with more than one condition. For example, if a stillbirth had a potential predictor of fetal death, usually maternal hypertension, antepartum haemorrhage or SGA, but also had histological or PCR evidence of infection in the placenta, cord or fetal blood or tissues based on data following delivery, we often did not know if the organisms identified reached their destination before or after the death occurred or were contaminants acquired during tissue sampling. To deal with this challenge, we made the following assumptions. First, that chorioamnionitis alone would not be considered a cause of stillbirth and did not influence preventability. Second, for an infection to be considered a cause of stillbirth, making the case non-preventable, an organism would need to be found in two or more fetal locations (e.g. brain and blood or liver and lung). If an organism was found only in one location, such as lung, histological evidence of inflammation in that same organ was needed for infection to be considered a non-preventable cause of death. Also, if histological funisitis was found on umbilical cord histology, for infection to be considered a non-preventable cause of stillbirth, the cord blood would need to be positive for a causative organism. These distinctions are important, because if an infection were identified postpartum as a cause of death, even in the presence of fetal growth restriction or hypertension, the death would not be considered preventable.

Potentially preventable stillbirths

We considered all stillbirths of any gestational age ≥20 weeks as potentially preventable that were associated with a vaccine-preventable infection, maternal syphilis, maternal malaria and/or a maternal haemoglobin of <7 g/dL in the absence of antenatal haemorrhage (Table 1B). The rationale was that vaccine-preventable infections, malaria and syphilis and severe maternal anemia are associated with stillbirth, diagnosable during prenatal care and should generally be preventable regardless of gestational age. For stillbirths occurring in pregnancies at ≥28 weeks of gestation and birthweight ≥1000 g, we then defined the conditions associated with potential preventability (Table 1C). These conditions include prolonged labour, ruptured uterus, umbilical cord accidents, SGA, placental abruption and placenta praevia, those with medical complications including diabetes and hypertensive disorders, those deaths occurring after hospital admission and those associated with delivery at ≥41 weeks of gestation. We considered stillbirths occurring at ≥28 weeks of gestation and birthweight ≥1000 g in the presence of antepartum haemorrhage as being potentially preventable.

We also performed a similar analysis on stillbirths with a gestational age of 24–27 weeks or weighing 500–999 g to assess potential preventability if these births had occurred in locations with excellent neonatal care and high survival of preterm infants delivered early to prevent a stillbirth (Table 1D).

In summary, Table 1A shows the conditions considered not preventable in LMIC or HIC with the exception of the conditions noted in Table 1B. Table 1C shows the conditions considered potentially preventable in LMIC (at ≥28 weeks of gestation and birthweight ≥1000 g), and Table 1D shows the conditions considered potentially preventable in stillbirths that occurred at 24–27 weeks of gestation and/or who weighed 500–999 g.

Results

From July 2018 through February 2020, at both sites, we screened 1453 women with stillbirths. Of these, 130 were ineligible because of a stillbirth that did not meet the 20-week gestation cutoff criteria (n = 51), 500-g birthweight cutoff where gestational age was missing (n = 7) or inability to complete screening (n = 72). Of those screened, 339 did not consent. Of the 984 participants with a stillbirth enrolled, the following were excluded from preventability analyses: 58 had insufficient information to judge preventability, 51 women had a multiple pregnancy and three withdrew. As a result, 872 women were deemed eligible for the preventability study (357 from the Indian site and 515 from the Pakistani site) (Figure 1).

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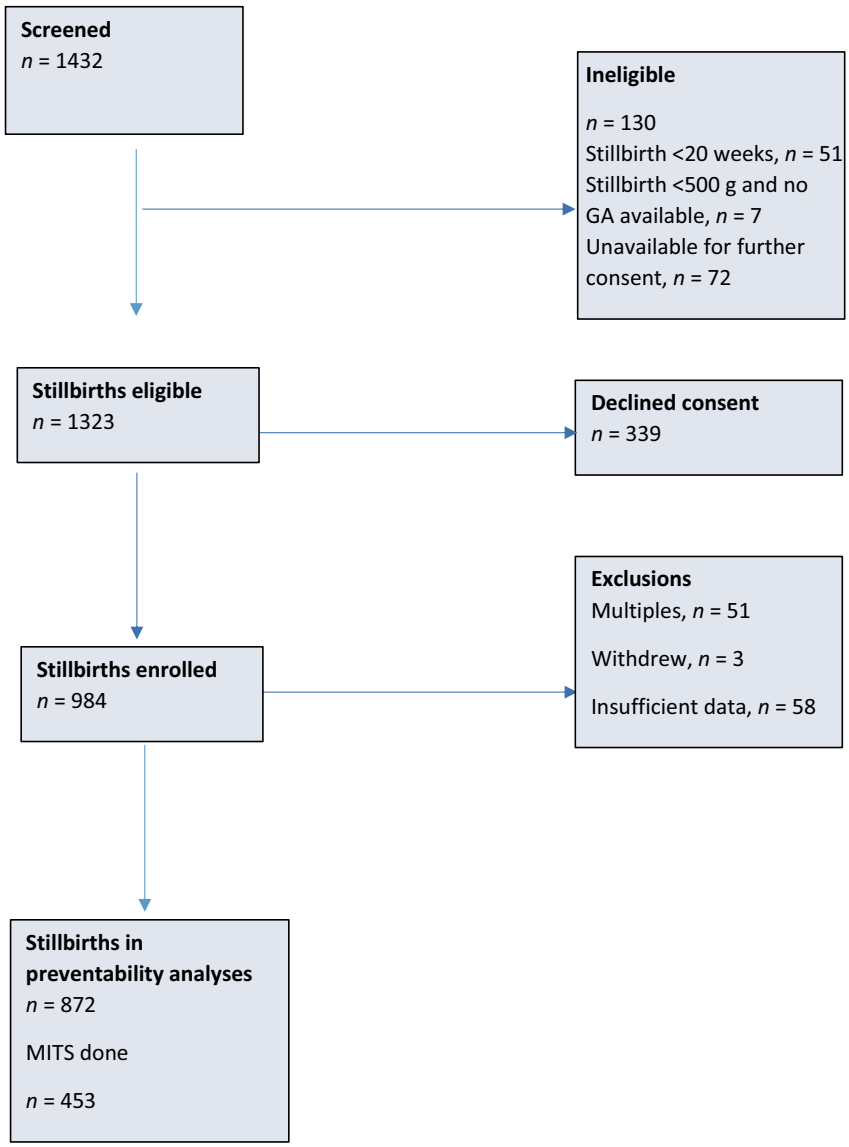

Figure 1. Enrollment Flow Chart.

The characteristics of the 872 mothers and the stillbirths are summarised by site and preventability status (Table 2). Most women in both sites were 20–30 years old, although the Pakistani site had a greater percentage of women >30 years of age compared with the Indian site (127/515; 24.7% versus 34/357; 9.5%). The women's occupation in both sites was predominantly given as homemaker. Compared with women in Pakistan, those in India had more education, were more likely to be primigravid, and received more antenatal care. Overall, among the women with stillbirths, 350/872 (40.1%) had hypertension and 193/872 (22.1%) had antepartum haemorrhage. In total, 453/872 (51.9%) mothers of stillbirths consented to minimally invasive tissue sampling.

Table 2 also presents characteristics of the stillbirths including birthweight, gestational age distributions and the presence of SGA. Overall, of the stillbirths with known gestational age, 128/834 (14.7%) were <28 weeks and of those with measured birthweight, 191/865 (21.9%) weighed <1000 g. Of stillbirths with a known gestational age and birthweight, the percentage with a birthweight for gestational age below the tenth centile using the Intergrowth-21 standard was 374/872 (42.9%). Most (670/872; 76.8%) of the stillbirths were known to be dead before labour and the other 202/872 (23.2%) died during the hospitalisation for delivery. In all, 463/772 (54.9%) were macerated.

The last four columns of Table 2 summarise these characteristics by site and whether the cases were judged

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Table 2. Maternal and stillbirth characteristics for India and Pakistan and by preventability status

	Overall			India		Pakistan	
	Total	India	Pakistan	Preventable	Not preventable	Preventable	Not preventable
Study population, *N*	872	357	515	187	170	297	218
Maternal age (years), *n* (%)							
<20	52 (6.0)	26 (7.3)	26 (5.0)	16 (8.6)	10 (5.9)	13 (4.4)	13 (6.0)
20–30	657 (75.3)	296 (82.9)	361 (70.1)	153 (81.8)	143 (84.1)	198 (66.7)	163 (74.8)
>30	161 (18.5)	34 (9.5)	127 (24.7)	18 (9.6)	16 (9.4)	86 (29.0)	41 (18.8)
Maternal education, *n* (%)							
No schooling, illiterate	243 (27.9)	63 (17.6)	180 (35.0)	33 (17.6)	30 (17.6)	109 (36.7)	71 (32.6)
No schooling, literate	97 (11.1)	9 (2.5)	88 (17.1)	7 (3.7)	2 (1.2)	53 (17.8)	35 (16.1)
1–4 years	34 (3.9)	17 (4.8)	17 (3.3)	9 (4.8)	8 (4.7)	9 (3.0)	8 (3.7)
5–12 years	443 (50.8)	236 (66.1)	207 (40.2)	123 (65.8)	113 (66.5)	117 (39.4)	90 (41.3)
>12 years	46 (5.3)	29 (8.1)	17 (3.3)	14 (7.5)	15 (8.8)	6 (2.0)	11 (5.0)
Maternal occupation, *n* (%)							
Homemaker	821 (94.2)	322 (90.2)	499 (96.9)	172 (92.0)	150 (88.2)	289 (97.3)	210 (96.3)
Employed outside the home	49 (5.6)	34 (9.5)	15 (2.9)	15 (8.0)	19 (11.2)	7 (2.4)	8 (3.7)
Gravida, *n* (%)							
0	296 (33.9)	155 (43.4)	141 (27.4)	87 (46.5)	68 (40.0)	70 (23.6)	71 (32.6)
1–3	414 (47.5)	187 (52.4)	227 (44.1)	90 (48.1)	97 (57.1)	126 (42.4)	101 (46.3)
≥3	162 (18.6)	15 (4.2)	147 (28.5)	10 (5.3)	5 (2.9)	101 (34.0)	46 (21.1)
Antenatal care received	795 (91.2)	354 (99.2)	441 (85.6)	184 (98.4)	170 (100.0)	249 (83.8)	192 (88.1)
Hypertensive disorders	350 (40.1)	141 (39.5)	209 (40.6)	93 (49.7)	48 (28.2)	145 (48.8)	64 (29.4)
Diabetes mellitus	39 (4.5)	11 (3.1)	28 (5.4)	7 (3.7)	4 (2.4)	24 (8.1)	4 (1.8)
Antepartum haemorrhage	158 (18.1)	61 (17.1)	97 (18.8)	47 (25.1)	14 (8.2)	77 (25.9)	20 (9.2)
Gestational age (weeks), *n* (%)							
20.0–23.6	35 (4.0)	17 (4.8)	18 (3.5)	0 (0.0)	17 (10.0)	3 (1.0)	15 (6.9)
24.0–27.6	93 (10.7)	39 (10.9)	54 (10.5)	1 (0.5)	38 (22.4)	0 (0.0)	54 (24.8)
28.0–31.6	186 (21.3)	82 (23.0)	104 (20.2)	28 (15.0)	54 (31.8)	47 (15.8)	57 (26.1)
32.0–36.6	287 (32.9)	106 (29.7)	181 (35.1)	75 (40.1)	31 (18.2)	130 (43.8)	51 (23.4)
≥37	233 (26.7)	112 (31.4)	121 (23.5)	82 (43.9)	30 (17.6)	91 (30.6)	30 (13.8)
Birthweight (g), *n* (%)							
<500	38 (4.4)	14 (3.9)	24 (4.7)	0 (0.0)	14 (8.2)	2 (0.7)	22 (10.1)
500–999	153 (17.5)	82 (23.0)	71 (13.8)	1 (0.5)	81 (47.6)	1 (0.3)	70 (32.1)
1000–1499	204 (23.4)	79 (22.1)	125 (24.3)	55 (29.4)	24 (14.1)	85 (28.6)	40 (18.3)
1500–2499	296 (33.9)	112 (31.4)	184 (35.7)	90 (48.1)	22 (12.9)	133 (44.8)	51 (23.4)
≥2500	174 (20.0)	70 (19.6)	104 (20.2)	41 (21.9)	29 (17.1)	72 (24.2)	32 (14.7)
Maceration present, *n* (%)	479 (54.9)	217 (60.8)	262 (50.9)	103 (55.1)	114 (67.1)	151 (50.8)	111 (50.9)
Known to be dead before delivery, *n* (%)	670 (76.8)	311 (87.1)	359 (69.7)	167 (89.3)	144 (84.7)	208 (70.0)	151 (69.3)
Small for gestational age, *n* (%)	374 (42.9)	181 (50.7)	193 (37.5)	116 (62.0)	65 (38.2)	137 (46.1)	56 (25.7)

preventable or not. For many of the demographic characteristics, the differences were small. However, for characteristics that played a role in the preventability determination, including hypertension, haemorrhage, SGA and diabetes, each was more common among those with preventable stillbirths. Stillbirths at an earlier gestational age and lower birthweights were less likely to be judged preventable, whereas those >28 weeks of gestation or with a birthweight >1000 g were more likely to be considered preventable.

Table 3 shows the reasons that stillbirths in the Indian and Pakistani sites were considered non-preventable. Of the 388 non-preventable stillbirths, 170 occurred in India and 218 occurred in Pakistan. Overall, most were considered not preventable because of gestational age <28 weeks and/or a birthweight <1000 g (217/388; 55.9%) – 100/170 (58.8%) in India and 117/218 (53.7%) in Pakistan. In addition, overall, 66/388 (17.0%) stillbirths were considered non-preventable because of a major congenital anomaly and 68/388 (17.5%) because of an undiagnosable/untreatable fetal infection, and 99/370 (25.5%) mothers had no signs or symptoms to alert the caregiver to a potential stillbirth. Because a stillbirth may have been judged non-

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Table 3. Reasons for stillbirths being considered not preventable in India and Pakistan

Variable	Overall	India	Pakistan
Stillbirths with preventability determined, *n*	872	357	515
Potentially preventable, *n* (% of stillbirths)	484 (55.5)	187 (52.4)	297 (57.7)
Not preventable, *n* (% of stillbirths)	388 (44.5)	170 (47.6)	218 (42.3)
Reasons not preventable *n* (% of preventable)			
Major anomalies	66 (17.8)	26 (16.0)	40 (19.2)
Non-identifiable/treatable infection	68 (18.4)	32 (19.8)	36 (17.3)
No signs of impending stillbirth	99 (25.5)	31 (22.9)	60 (27.5)
<1000 g and/or <28 weeks of gestation without discoverable, preventable conditions*	217 (58.6)	100 (61.7)	117 (56.3)

*Discoverable, preventable conditions include vaccine-preventable infection, maternal syphilis, maternal malaria and low haemoglobin with no evidence of bleeding.

Table 4. Stillbirths considered preventable at >28 weeks of gestation and/or >1000 g birthweight

Variable	Overall	India	Pakistan
Stillbirths at ≥28 weeks of gestation and birthweight ≥1000 g, *n* (%)	649	255	394
Potentially preventable at gestational age ≥28 weeks and birthweight ≥1000 g, *n* (% of stillbirths ≥28 weeks and ≥1000 g)*	478 (73.5)	185 (72.5)	293 (74.4)
Reasons for preventability, *n* (% of preventable at ≥28 weeks/≥1000 g)			
Small for gestational age**	252 (52.8)	116 (63.0)	136 (46.4)
Hypertension	240 (50.2)	95 (51.6)	145 (49.5)
Antepartum haemorrhage	150 (31.4)	50 (27.2)	100 (34.1)
Death after hospital admission	75 (15.7)	35 (18.9)	40 (13.7)
Diabetes	32 (6.7)	7 (3.8)	25 (8.5)
Post-dates (≥41 weeks)	25 (5.2)	12 (6.5)	13 (4.4)
Prolonged labour	22 (4.6)	2 (1.1)	20 (6.8)
Low haemoglobin without evidence of bleeding	17 (3.6)	3 (1.6)	14 (4.8)
Cardiac disease	8 (1.7)	0 (0.0)	8 (2.7)
Thyroid disease	7 (1.5)	3 (1.6)	4 (1.4)
Diagnosable/treatable maternal infection	7 (1.5)	4 (2.2)	3 (1.0)
Umbilical cord accident	6 (1.3)	2 (1.1)	4 (1.4)
Maternal syphilis	6 (1.3)	3 (1.6)	3 (1.0)
Maternal malaria	3 (0.6)	1 (0.5)	2 (0.7)
Red blood cell abnormality	1 (0.2)	0 (0.0)	1 (0.3)
Oligohydramnios	1 (0.2)	1 (0.5)	0 (0.0)
Vaccine-preventable infection	1 (0.2)	1 (0.5)	0 (0.0)

*A stillbirth may be considered preventable for more than one reason so the sum will equal more than 100%.
**SGA is defined as birthweight less than the INTERGROWTH-21ST tenth centile weight, which is not available for gestational age <24 weeks or ≥43 weeks and fetuses missing sex or birthweight.

preventable for several reasons, the sum of responses adds up to >100%.

Table 4 displays preventability status of the 649 stillbirths who were ≥28 weeks of gestation and/or ≥1000 g birthweight. Of these, 255 occurred in India and 394 occurred in Pakistan. Overall, 478/649 (73.7%) were considered potentially preventable, 185/255 (72.5% of the Indian site stillbirths) in India and 293/394 (74.4% of the Pakistani site stillbirths) in Pakistan. Because a single case could be classified as preventable for multiple reasons, the sum is >100%. The three most common reasons that stillbirths were judged potentially preventable included SGA (252/478; 52.7%), maternal hypertensive disease (240/478; 50.2%) and maternal antepartum haemorrhage (150/478; 31.4%). There were 75 stillbirths ≥28 weeks of gestation and ≥1000 g that occurred after hospital admission with a live fetus accounting for 75/478 (15.7%) of the preventable cases. All but one of these deaths were also identified as

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potentially preventable by the presence of other conditions. Much less common were conditions such as maternal diabetes (32/478; 6.7%), prolonged labour (22/478; 4.6%) and post-dates (25/478; 5.2%). No other condition was present in ≥4% of the stillbirths considered potentially preventable. Six stillbirths were <28 weeks of gestation and/or birthweight <1000 g that were deemed potentially preventable. Of those, the primary reason (4/6) was a low haemoglobin level independent of haemorrhage, with one each due to syphilis and malaria (data not shown).

Most stillbirths at 24–27 weeks of gestation and or birthweight 500–999 g were defined as not preventable because in these sites, even if delivered alive and given NICU care, these infants rarely survive. In settings with advanced NICU care, most infants born at 24–27 weeks of gestation survive. We therefore investigated which stillbirths at 24–27 weeks of gestation and/or birthweight 500–999 g would be potentially preventable based on the criteria applied to ≥28 week / ≥1000 g infants.

Table 5 shows the analysis of the 24–27 weeks of gestation and/or birthweight 500–999 g group to simulate what could be possible if the resources and level of NICU care approximated those in HIC settings. Of the 192 stillbirths delivered in both sites at 24–27 weeks of gestation and/or birthweight 500–999 g, 136 (70.8%) were deemed potentially preventable. Similar to the pregnancies defined by the ≥28 weeks / ≥1000 g cutoff, SGA 80/136 (58.8%), hypertension 81/136 (59.6%) and antepartum haemorrhage 43/136 (31.6%) were the most common conditions thought to be discoverable and treatable, making the associated stillbirth potentially preventable. Stillbirths at 24–27 weeks of gestation and/or birthweight 500–999 g who had a fetal heartbeat heard on admission were categorised as potentially preventable and accounted for 25/136 (18.4%) of preventable stillbirths in this gestational age group. Each of these stillbirths was also identified as preventable by the presence of other conditions. There were 56 stillbirths at 24–27 weeks of gestation and/or birthweight 500–999 g deemed not preventable, mostly because of the presence of major anomalies (25/56; 44.6%), non-treatable infections (14/56; 25.0%) and because no evidence of stillbirth risk was ascertained (17/56; 30.3%) (data not shown).

In a separate analysis, we analysed the panel members' responses to whether the stillbirth cases were potentially preventable. Data from this analysis showed that overall, the panel members believed that 63.8% of the stillbirths were preventable. For stillbirths at ≥28 weeks / ≥1000 g, 73.5% were considered preventable by the panel members, whereas only 22.0% of stillbirths at 24–27 weeks of gestation and/or birthweight 500–999 g were categorised by panel members as potentially preventable (data not shown).

Table 5. Stillbirths deemed not preventable and potentially preventable at 24–27 weeks of gestation and/or birthweight 500–999 g

Variable	Overall	India	Pakistan
Stillbirths at 24–27 weeks of gestation and/or birthweight 500–999 g, *n*	192	90	102
Not preventable, *n* (%)	56 (29.2)	27 (30.0)	29 (28.4)
Reasons not preventable*, *n* (% of not preventable at 24–27 weeks and/or 500–999 g)			
Major anomalies	25 (44.6)	12 (44.4)	13 (44.8)
Non-identifiable/treatable infection	14 (25.0)	6 (22.2)	8 (27.6)
No cause determined/no preventable conditions identified	17 (30.3)	9 (33.3)	8 (27.6)
Potentially preventable, *n* (%)	136 (70.8)	63 (70.0)	73 (71.6)
Reasons preventable*, *n* (% of preventable at 24–27 weeks and/or 500–999 g)			
Small for gestational age**	80 (58.8)	43 (68.3)	37 (50.7)
Hypertension	81 (59.6)	38 (60.3)	43 (58.9)
Placental abruption or placenta praevia	43 (31.6)	15 (23.8)	28 (38.4)
Death after hospital admission	25 (18.4)	17 (27.0)	8 (11.0)
Diabetes	7 (5.1)	3 (4.8)	4 (5.5)
Cardiac disease	4 (2.9)	2 (3.2)	2 (2.7)
Low haemoglobin with no evidence of bleeding	2 (1.5)	2 (3.2)	0 (0.0)
Thyroid disease	2 (1.5)	2 (3.2)	0 (0.0)
Maternal syphilis	1 (0.7)	0 (0.0)	1 (1.4)
Diagnosable/treatable maternal infection	1 (0.7)	1 (1.6)	0 (0.0)
Umbilical cord accident	1 (0.7)	1 (1.6)	0 (0.0)
Oligohydramnios	1 (0.7)	1 (1.6)	0 (0.0)

*A stillbirth may have more than one reason so the sum will equal more than 100%.
**SGA is defined as birthweight less than the INTERGROWTH-21ST tenth centile weight, which is not available for gestational age <24 weeks or ≥43 weeks and fetuses missing sex or birthweight.

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Discussion

Main findings

In this study, of 872 stillbirths in India and Pakistan at 20 weeks of gestation or more, 57.5% were deemed to be potentially preventable, assuming most stillbirths before 28 weeks of gestation and/or <1000 g were generally not preventable. Of stillbirths ≥28 weeks of gestation and birthweight ≥1000 g, 73.5% were considered potentially preventable. Following the gestational age/birthweight cutoffs, the most common reasons for a stillbirth not being considered potentially preventable were the presence of a major congenital anomaly, an undiagnosable fetal infection and no signs before delivery to alert the clinician to a potential stillbirth.

By far, the most common conditions associated with a potentially preventable stillbirth at ≥28 weeks of gestation and birthweight ≥1000 g were SGA (52.7%), maternal hypertension (50.2%) and antenatal haemorrhage (31.4%). Stillbirths free of anomalies and undiagnosable infections that occurred in labour accounted for 15.7% of the preventable stillbirths, but virtually all were also deemed preventable because of the presence of other conditions.

For fetal deaths at 24–27 weeks of gestation and/or birthweight 500–999 g, the same conditions were even more common: 58.8% for SGA, 59.6% for maternal hypertension and 31.6% antenatal haemorrhage, respectively. Preventable stillbirths that occurred after hospital admission accounted for 18.4% of the preventable stillbirths in this gestational age and birthweight range. Therefore, we believe that many of these stillbirths would have been preventable in locations where excellent NICU care would have allowed survival of these infants, had they been delivered alive.

Interventions to reduce stillbirths associated with SGA, hypertension and antepartum haemorrhage as well as intrapartum deaths are not complicated or expensive and should be available within a functional perinatal healthcare system.[6,8,10] 'System' is emphasised because these interventions require a continuum of care including high-quality prenatal care, transportation to a higher-level facility, monitoring in labour and access to caesarean section. In prenatal care, low-dose aspirin should prevent some of the deaths from pre-eclampsia/eclampsia.[19] Blood pressure and fetal growth monitoring will determine those at risk from pre-eclampsia/eclampsia and/or with growth restriction.[8,10] Placenta praevia is discoverable by ultrasound. An appropriately timed caesarean section for pre-eclampsia and haemorrhage and some of the other conditions should prevent most of the stillbirths in fetuses discovered to be at risk.[20]

Although we had extensive placental and fetal tissue histological and PCR data to evaluate the cause of the stillbirth, none of these data were available before delivery for the clinicians with the potential to intervene to prevent the stillbirth. Hence, this study is distinct from a parallel cause-of-death stillbirth study that often uses data obtained after delivery.[12] In many cases, information after delivery could lead us to judge a stillbirth as non-preventable. However, for a stillbirth to be deemed preventable, the only data collected postpartum used for this purpose were data used to determine SGA, based on the assumption that SGA diagnosed by an ultrasound examination in the second or third trimester could lead to fetal monitoring and early delivery to prevent the stillbirth.

As there is strong evidence that placental maternal vascular malperfusion is a precursor to each of the three conditions seen so commonly as a cause of stillbirth and which informed much of the basis of our thinking about preventability, we believe it crucial to find ways to prevent this condition.[21–24] However, in the meantime, it is important to develop methodologies to discover evidence of vascular malperfusion as early in the pregnancy as possible in order to monitor the pregnancy so that appropriate steps may be taken to prevent the stillbirth by timely delivery.[25–29]

Strengths and limitations

We are aware that there are interventions that may reduce stillbirths that were excluded from this analysis. For example, we did not assess non-medical interventions that were not specifically aimed at preventing stillbirth. These include the impact of community interventions such as those aimed at improving the standard of living, or improving overall nutritional status, or providing increased access to education for women, and family planning. Certain maternal behaviours such as tobacco, alcohol and other drug use are potentially amenable to interventions and reducing these behaviors should prevent some stillbirths. Obesity is also an important risk factor for stillbirth in HIC and it is likely that weight reduction in obese women before pregnancy would eliminate some stillbirths.[29] As another example, some neural tube defects are preventable with supplemental folic acid, and a folic acid supplementation programme would probably prevent some stillbirths.[30] However, the relationships between these conditions and behaviours and fetal death are difficult to prove in specific cases. Accordingly, stillbirths associated with these conditions or behaviours were not considered as potentially preventable in this study.

There are several strengths and weaknesses in this study. Among the strengths are that a large number of stillbirths were evaluated, that the study was performed prospectively in two countries with a range of quality of care, and that there were abundant data available to inform the clinical consideration about stillbirth preventability. Although the Pakistani and Indian sites performed the study independently (with central guidance), the results for each site

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regarding prevalence of conditions and percent of cases judged preventable were similar. Interestingly, the percent of cases deemed preventable by the panel members was virtually identical to the percent preventable by the study criteria.

Weaknesses include that the participants were recruited at delivery and some of the information related to prenatal events was based on the mothers' recall or medical records. For this reason, we were unable to consistently differentiate between various types of hypertensive disorders or reasons for maternal haemorrhage. We also acknowledge that non-medical causes of stillbirth are important, but as noted, this was beyond the scope of this analysis. An overall issue is that the classification of the stillbirths into preventable and non-preventable cases was based on a set of criteria that were arbitrarily established. Although the classification system was generally concordant with the recommendations of in-country practitioners, we understand that other criteria could have been justified and adopted. We tried to make our criteria as transparent as possible. An important limitation is uncertainty regarding the diagnosis of SGA. We based this classification on neonatal birthweight centiles for gestational age. However, gestational age dating was not always certain and many women did not have early obstetric sonograms. In addition, there was probably a meaningful interval between death of the fetus and delivery in some cases. Accordingly, we may have overestimated the contribution of SGA to preventable stillbirths.

Interpretation

In recent years, the focus on stillbirth risk factors and causes of demise has increased dramatically with most attention focused on stillbirths in HIC.[29] Limited attention has been given to stillbirths in LMIC and less on which stillbirths were actually preventable. One approach focused on whether the stillbirth occurred near delivery (defined by absence of maceration) and the birthweight and or gestational age, concluding that in LMIC many stillbirths were not macerated and weighed more than 2000 g and were therefore preventable with improved quality of care.[3,5] Other studies have modelled the stillbirths potentially averted with implementation of a range of evidence-based interventions, including immunisations, nutritional supplements and screening for syphilis, which are often unavailable to pregnant women in LMIC settings.[9–12] For this study, we built upon the evidence for preventable conditions and evaluated a specific population of stillbirths to determine which medical conditions amenable to discovery before delivery were present, making the stillbirth potentially preventable. It is noteworthy that studies using many different designs focused on LMIC concluded that the majority of stillbirths were potentially preventable.

Conclusions

This study, performed in two LMIC, found that most stillbirths were preventable and were most often associated with maternal hypertension, antepartum haemorrhage and SGA as well as asphyxia in labour. Appropriate obstetric care including antenatal and intrapartum screening for these conditions, including fetal heart rate monitoring in labour and utilisation of an appropriate intervention, often involving caesarean delivery, could potentially prevent many of these stillbirths. Research to prevent the placental pathology (maternal vascular malperfusion) often underlying these conditions has great potential to identify interventions to reduce stillbirths.[22–24]

Disclosure of interests

The authors disclose no conflicts of interests. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

EMM and RLG conceived the study analyses with input from RMS. SS, SSG, EMM and RLG developed the protocol with input from RMS, GG, SY, HY, MS and SSu. SD, SSu, GG, SY, HY, KB and MS oversaw the study implementation. KH, AA and LP performed the statistical analyses. All authors provided feedback on the draft and approved the final version.

Details of ethics approval

The study was approved by the Ethics Committee at each site, at the institutions of the US sites, and by Research Triangle international. The study was registered with the Clinical Trial Registry of India (CTRI/2018/03/012281).

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

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