

Bharti Sharma, Neelam Aggarwal*, Vanita Suri, Sujata Siwatch, Nandita Kakkar and Sundaram Venkateshan

Facility-based stillbirth surveillance review and response: an initiative towards reducing stillbirths in a tertiary care hospital of India

<https://doi.org/10.1515/jpm-2021-0440>

Received August 31, 2021; accepted February 7, 2022;

published online March 2, 2022

Abstract

Objectives: India has the highest number of stillbirths in the world in 2019, with an estimated stillbirth rate of 13.9 per 1,000 births. Towards better identification and documentation, a stillbirth surveillance pilot was initiated with the World Health Organization Southeast Asia collaboration in Northern India in 2014. This study aimed to assess whether stillbirth surveillance is feasible and whether this approach provides sufficient information to develop strategies for prevention.

Methods: This study followed the framework provided in “WHO Making Every Baby Count” in which mortality audit is conducted in six steps; (1) identifying cases; (2) collecting information; (3) analysis; (4) recommending solutions; (5) implementing solutions; and (6) evaluation.

Results: A total of 5,284 births were examined between December 2018 and November 2019; 266 stillbirths were identified, giving a stillbirth rate of 50.6 per 1,000 births in a tertiary care referral hospital of northern India. Out of 266 stillbirths, 223 cases were reviewed and recommendations were formulated to strengthen obstetric triage, implementing fetal growth charts, strengthen the existing referral system and improve the communication skills of health care providers for better compliance with clinical practice guidelines.

Conclusions: Conducting stillbirth surveillance review and the response of cases in low-middle income countries setting is feasible. As countries progress towards ending preventable mortality, this has the potential to serve as a key process in improving evidence-based and context-specific planning and preventive strategies towards improving the quality of care.

Keywords: cause of death; stillbirth; stillbirth audit; stillbirth rate.

Introduction

Worldwide in 2019, nearly 2.0 million babies were stillborns and about half of them occur in six countries and India is one among them [1, 2]. There is substantial variation in stillbirth rates across countries, the highest stillbirth rate reported is 32.3 per 1,000 births whereas the lowest is 1.4 per 1,000 births [2]. The stillbirth rate of India is 13.9 per 1,000 births in 2019 with wide interstate variation [2]. In spite of such a huge burden of stillbirths, global attention towards stillbirth is insufficient and the annual reduction rate for stillbirth is far behind the maternal or under five child mortality rates [1]. The every newborn action plan (ENAP) was endorsed by United Nations to every country to reduce the stillbirth burden and to achieve the stillbirth rate of 12 or fewer per 1,000 births by 2030 [3]. ENAP also recommends improving the perinatal death (stillbirth + neonatal deaths) registration, investigation to assign the cause of death, identification of modifiable risk factors and implementation of high quality national audits. Suboptimal care has been found unacceptably high according to the recent reports from the countries where national perinatal audit programmes have been achieved a reduction in stillbirth rate [3, 4].

Following ENAP, India also set the single digit stillbirth target for 2030 under INAP (Indian newborn action plan), first national stillbirth prevention target [5]. In India, the pilot Stillbirth surveillance was initiated from July 2014; through a joint collaboration between WHO Regional Office for South-East Asia (SEARO) and CDC, USA under the

*Corresponding author: Dr. Neelam Aggarwal, Professor, Department of Obstetrics & Gynecology, PGIMER, Chandigarh, 160012, India, Phone: 0172 2756331, E-mail: drneelamaggarwal@gmail.com

Bharti Sharma, Vanita Suri and Sujata Siwatch, Department of Obstetrics & Gynecology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Nandita Kakkar, Department of Histopathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Sundaram Venkateshan, Department of Pediatrics (Neonatology), Post Graduate Institute of Medical Education and Research, Chandigarh, India

SEAR-NBBD initiative along with newborns birth defect surveillance. A network of hospitals with high delivery load was identified to report stillbirths under the integrated newborn birth defects (NBBD) database, with the aim to establish a National Network of institutions in India. In order to plan further preventive strategies this project was further extended beyond counting numbers, to start auditing each fetal death on the basis of 'Making Every Baby Count' recommendations on perinatal audits [6]. Stillbirth review and response is also a type of medical audit, involves the systematic review of each fetal death and to critically analyze the modifiable factors contributing to stillbirth. The primary objective of stillbirth review and response is to improve the quality of patient care, formulate the appropriate actions to address the modifiable factors, implement and achieve the goal of ending preventable stillbirths [7]. This study presents the process of stillbirth audit (review and response) in a tertiary care referral hospital of Northern India and the recommendations made.

Materials and methods

Study area

The study was conducted in the department of Obstetrics & Gynecology, PGIMER Chandigarh, India over a period of one year from December 2018 to November 2019. A stillbirth was defined as the delivery of a baby showing no sign of life beyond 20 weeks of gestation or birth weight of 500 g or more [8]. The maternal demographic, obstetric history, medico surgical history, number of antenatal visits, clinical details and investigations were collected from the clinical records. The delivery notes were reviewed and along with baby details, any other relevant findings were also noted. The cause for each fetal death was assigned as per International Classification of Death Perinatal Mortality (ICD-PM) System of classification which includes the type of stillbirth (antepartum/intrapartum), associated maternal and fetal condition relevant at the time of fetal death [9]. The six step mortality audit cycle was followed for stillbirth review and response as recommended by WHO in following steps:

Step 1: Identifying cases

All the deliveries were identified in the institute and recorded from the labor room, emergency areas including intensive care units. The data was paper based and collected from delivery registers, verified with records maintained by nurses in labor room, emergency area, Operation Theater and ICUs. Because of high load of stillbirth in our setup out of identified cases, stillbirths of 1,000 g or gestation of 28 weeks or more (WHO definition) were selected for further detailed review after taking informed consent [10].

Step 2: Collecting information

The thematic cases were systematically reviewed and information was recorded on pre structured questionnaire which was prepared according to the key information for facility based review outlined in making every baby count book [6]. The demographics, history, clinical records and antenatal investigations were noted for maternal

information. The delivery notes were reviewed for intrapartum details, gestation age, birth weight, fetal and placental examination finding and other. The denominators for each month were also collected which included total births, live births, stillbirths, neonatal deaths, maternal deaths, maternal near miss, cesarean rate and number of low birth weight babies (<2,500 g). The cases were reviewed before the discharge and preferably within a week of the event. The information on modifiable factors, contributory factors and barrier to care was extracted by reviewing the clinical records, referral slips and conducting in-depth interviews of patients and their husbands or other family members wherever possible. The most probable cause for each stillbirth was assigned as per ICD-PM system of classification based on available history and investigations [9]. These data was collected by doctor and medical social worker and entered in the statistical software freely available online (Epi info version seven Centers for Disease Control and Prevention, Atlanta, GA, USA) and quality of data was assured by frequent validity checks.

Step 3: Analysing information

Every month qualitative and quantitative analysis of the data was performed by the stillbirth audit team and different rates which include stillbirth rate, maternal mortality rate, cesarean rate, maternal near miss were calculated. The trends analysis of proportion of intrapartum stillbirths over a year was done using Mann-Kendall trend test. The qualitative analysis of the data was done to identify the modifiable factors or associated factors attributed to stillbirths. The criterion for selecting individual cases was to look for missed opportunities or modifiable factors or latest recommendation in management which could have been rectified to improve the quality of care provided. The objective of Individual case discussion was to bring the individual responsibility and sense of ownership to the whole department. The latest literature related to management of particular case was discussed to improve the quality of health care. The factors related to administrative level like weak referral system, non availability of neonatal intensive care unit were also discussed.

Steps 4, 5, 6: Recommending solutions, implementation and evaluating and refining

To formulate appropriate recommendations is the most challenging part of review process. After analyzing the each selected case quantitatively and qualitatively, looking in the modifiable factors in details, recommendations were made after monthly perinatal meetings. In our institute monthly perinatal meetings are attended by the whole faculty of obstetric and neonatology department including residents.

Results

From December 2018 to November 2019, 266 stillbirths delivered out of 5,248 births with a stillbirth rate of 50.6 per 1,000 births. Of these stillbirths 43 (16.2%) occurred before 28 weeks and 223 (83.8%) after 28 weeks, yielding a late stillbirth rate of 42.5 per 1,000 births. These stillbirths were identified from delivery register and verified with nursing officer's records as per institutional protocol all deliveries occurring in labor room, operation theater, ICUs, HDU or Burn ward are being reported to labor room team and recorded in delivery register and nursing officer's registers.

The demographical and clinical characteristics of stillbirth >28 weeks (n=223) are depicted in Table 1. The minimum perinatal indicators, six essential pieces of information were collected for each stillbirth, includes maternal age, mode of delivery, birth weight, gestational age, birth outcome and place of delivery. Monthly total live births, stillbirths, proportion of antepartum, intrapartum and neonatal death were also collected from labor room register and various rates were calculated for review i.e. stillbirth rate, neonatal mortality rate, intrapartum stillbirth rate, cesarean rate as depicted in Figure 1. The fall in proportion of intrapartum stillbirth over the months was observed during the study period, however it was not statistically significant (p value 0.1107). Table 2 shows the distribution of cause of death of 223 stillbirths according to ICD-PM System of classification. Maternal medical and surgical conditions were the most frequent (55.6%) followed by complications of placenta, cord and membranes (14.7%), maternal complications of pregnancy (9.4%). 65.5% (146/223) of stillbirths were antepartum i.e. fetal death occurred before the onset of labor, rest were intrapartum (34.5%). Antepartum hypoxia (A3=22.4%) and disorders related to fetal growth (A5=20.6%) were the commonest causes of antepartum stillbirths. Among intrapartum the acute intrapartum event (I3=14.8%) and disorder related to fetal growth (I6=10.3%) were the commonest cause assigned.

The modifiable factors were also compiled separately for antenatal and intrapartum period (Table 3). During antenatal the more frequent factors were no/late antenatal care, no knowledge of danger sign and non availability of delivery facilities during intrapartum period the commonest factors were reached late, delay in referrals and non availability of delivery facilities. Among these antepartum death, 44% women did not have knowledge of danger signs and failed to recognize the seriousness whereas 16% had no antenatal care. Examples of danger signs includes decreased fetal movement, headache (due to increased blood pressure), bleeding per vaginum for which women failed to recognize the seriousness before reaching a health care facility.

Among intrapartum stillbirths, only 4.48% of mother had complications during labour in our study, rest all were attributed to prematurity or low birth weight. Among them 12.9% of families refused for cesarean for fetal indication or neonatal care whereas in 19.5% NICU facilities were unavailable at that point of time (Table 3).

Out of these cases two or three cases were selected for detailed discussion in monthly perinatal meeting. The criteria for selecting cases were mainly where fetal heart was present on admission or who were adequately booked

Table 1: Demographic and clinical details of stillbirths.

Characteristics	Frequency, n (%)	Characteristics	Frequency, n (%)
Maternal age		Maternal medical history	
<20 years	49 (1.8%)	Yes	52 (23.3%)
20–35 years	204 (91.5%)	No	171 (76.7%)
>35 years	15 (6.7%)		
Education		Antenatal care	
Illiterate	12 (5.4%)	No	12 (5.4%)
Literate	211 (94.6%)	<4 ANC visits	57 (25.6%)
		4 or more ANC visits	154 (69.0%)
Parity		Number of hospital visited before reaching tertiary care	
0	111 (49.8%)	One	17 (7.6%)
1	68 (30.5%)	Two	117 (52.4%)
2 or more	44 (19.7%)	More than 2	89 (39.9%)
Previous stillbirth		Type of delivery	
No	210 (94.2%)	Vaginal delivery	205 (91.9%)
Previous 1 stillbirth	8 (3.6%)	Cesarean	18 (8.1%)
Previous 2 or more stillbirth	5 (2.2%)		
Birth control/contraception used before planning pregnancy		Gestational age	
Yes	5 (2.2%)	28–33 ⁺⁶ weeks	107 (47.9%)
No	218 (97.8%)	34–36 ⁺⁶ weeks	55 (24.7%)
		37–40 ⁺⁶ weeks	52 (23.3%)
		≥41 weeks	9 (4.0%)
Was birth plan made		Birth weight	
Yes	29 (13.0%)	<1000 g	48 (21.5%)
No	194 (87.0%)	1,000–2,500 g	138 (61.9%)
		>2,500 g	37 (16.6%)

ANC, antenatal visits.

supervised or where different or latest management could have reasonably made the difference in the outcome. Based on monthly perinatal meetings some recommendations were made and few of them were implemented as depicted in Table 4. Some of the changes in practices were as follows: (i) actively enquiring for pruritus to rule out cholestasis of pregnancy and considering early delivery in case of high fasting bile acids; (ii) performing ultrasound at around 34–36 weeks of gestation so as not to miss any fetal growth restriction in busy outpatient departments; (iii) established a triage in emergency area.

Number of deliveries	Dec 2018	Jan 2019	Feb 2019	March 2019	April 2019	May 2019	June 2019	July 2019	August 2019	Sep 2019	Oct 2019	Nov 2019	Total
Total births	548	594	428	459	436	463	569	622	550	543	565	580	5249
Live births	526	565	406	429	415	431	541	583	520	508	529	557	4973
Stillbirths	22	29	22	30	21	22	28	39	30	33	35	23	266
Antepartum	15	14	9	16	7	8	18	32	21	23	25	17	157
Intrapartum	7	15	13	14	14	14	10	7	9	10	10	6	109
Neonatal death	21	28	16	24	28	23	14	24	26	12	21	12	190
Maternal death	2	6	5	4	1	1	3	5	6	8	6	4	37
Maternal near miss	20	23	14	20	11	25	18	24	26	11	8	6	187
Number of cesarean section	210	233	178	192	197	207	256	250	204	237	230	232	2159
Number of instrumental deliveries	30	34	17	27	20	32	21	29	30	34	17	27	267
Number of babies born <2500 grams	237	273	159	109	198	184	249	287	240	228	239	245	1941

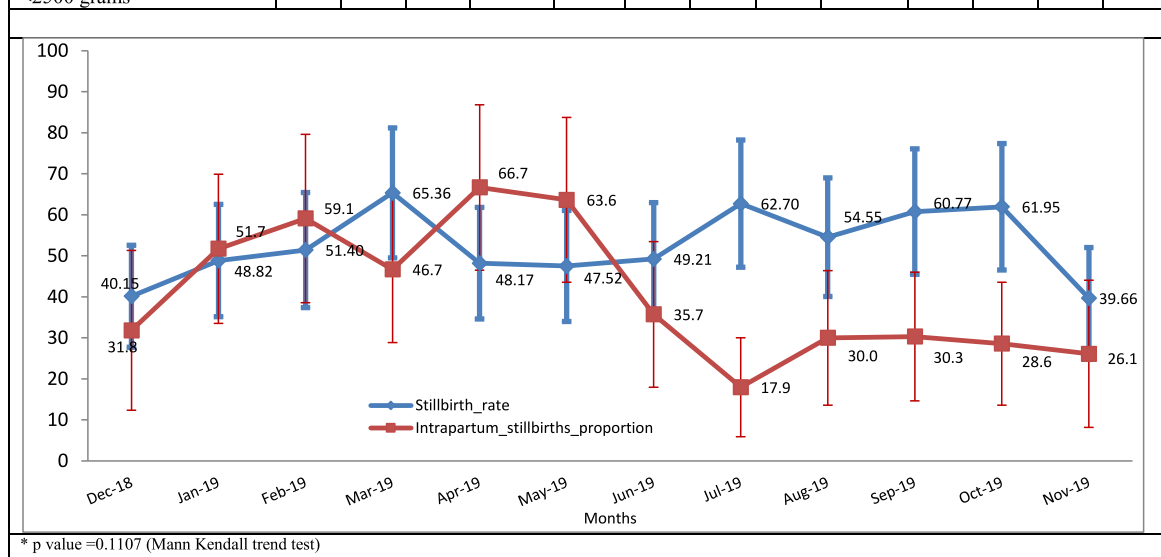


Figure 1: Trends of various monthly rates.

Discussion

This study shows a prototype of internal audit of the stillbirths delivered in a tertiary care level where not only the cause of fetal death was assigned, but the modifiable factors were also identified to plan the strategies to reduce the stillbirths further. The main objective of medical audits is improving the patient care, regular review of work and look for latest evidence based management for better outcome.

The important component of stillbirth audit is to assign the most appropriate cause of fetal death. Number of classifications have been recommended and tried in various settings, recently WHO have come up with ICD-PM System of classification [9]. This global system of classification is expected to facilitate the direct comparison irrespective of the settings. Based on the classification system (Table 1), majority of deaths were occurred in antepartum period which signifies the quality of antenatal care. Among antepartum, fetal death related to growth disorders were

maximum (46/146–31.5%) which further emphasizes the need of screening of FGR. It also highlights the quality of antenatal care being provided to our women.

In this study 34.5% of women had live fetus at the start of labour and had stillbirth during labour i.e. intrapartum stillbirth. Intrapartum deaths are those deaths which have occurred during labor irrespective of place of death. Globally 50% of stillbirths are intrapartum and the key area of prevention is quality intrapartum care [11]. If we look at the trends of intrapartum stillbirth over a year, there was a fall in proportion of intrapartum stillbirths (Figure 1) which can be considered as the impact of stillbirth audits and change in practice over the time. Similar reduction in intrapartum deaths have also been seen following national audits of high resources settings which reflects the improvement in quality of intrapartum care provided [7]. On further details, only a small proportion (4.48%) of mothers had complications during labour in our study, rest all were attributed to prematurity or low birth weight. So

Table 2: Distribution of cause of death of 223 stillbirths according to ICD-PM system of classification.

Type of death	Complications of placenta, cord and membranes M1 = 33 (14.7%)	Maternal complications of pregnancy M2 = 21 (9.4%)	Other complications of labour and delivery M3 = 10 (4.48%)	Maternal medical and surgical conditions; noxious influences M4 = 124 (55.6%)	No maternal condition identified—healthy mother M5 = 35 (15.6%)	Total = 223
Antepartum = 146 (65.5%)						
A1 (Birth defect)	1	1	0	8	13	23 (10.3%)
A2 (Infection)	0	0	0	0	0	0
A3 (Antepartum hypoxia)	15	3	1	31	0	50 (22.4%)
A4 (Other specified antepartum disorder)	1	1	0	4	1	7 (3.1%)
A5 (Disorder related to fetal growth)	1	6	0	38	1	46 (20.6%)
A6 (Unspecified cause of antepartum death)	2	3	0	8	7	20 (8.9%)
Intra partum = 77 (34.5%)						
I1 (Birth defect)	0	3	0	4	10	17 (7.6%)
I2 (Birth trauma)	0	0	0	0	0	0
I3 (Acute intrapartum event)	10	2	8	12	1	33 (14.8%)
I4 (Infection)	0	0	0	0	0	0
I5 (Other specified intrapartum disorder)	2	0	0	1	0	3 (1.3%)
I6 (Disorder related to fetal growth)	1	2	1	17	2	23 (10.3%)
I7 (Other)	0	0	0	1	0	1 (0.4%)
Total = 77						

ICD-PM, International Classification of Death Perinatal Mortality; A, antepartum; I, intrapartum; M, maternal condition.

along with quality intrapartum care, there is need to strengthen the neonatal services further to reduce these stillbirths in our settings.

In index study “avoidable” or “missed” opportunities were identified during audits in almost all the cases which might have made the difference in the outcome. On the contrary in national audits of high resource settings, avoidable factors do exist to half of the reviewed cases [7].

In our local audit the area of improvement identified include the quality of antenatal care, fetal growth restriction detection and screening, strengthening referral system, strengthening neonatal intensive care units and delivery facilities for preterm and low birth weight babies and improving the communication and skills of health care providers and increase the awareness of women in pregnancy.

These avoidable factors identified seems to be doable even at resource constrain setting to achieve the target of single digit stillbirth rate [12]. With such a huge burden, India definitely require national audits and new practice guidelines for prevention at large scale however local audits also gives an insight to each individual to work

better. LMICS can also learn and implement the interventions from the existing evidence from the achievements of HMICs in reducing our stillbirth burden further [13–15].

The limitation of this study is that we have not included the deaths occurring in the first neonatal week. We have also not correlated the placental pathology with each cause. Audit system is a time consuming and numbers of professionals are involved in managing these women as most of the cases in our study were referrals. So as such there is no external validation as we have evaluated associated factors from the referrals and enquired from patients and her families only.

Conclusions

This study demonstrates the feasibility of auditing stillbirths at facility level of a huge burden setting. It seems possible to implement the recommendations at local level which can further be used to plan intervention at regional level for reducing the preventable stillbirths further.

Table 3: Modifiable factors: barrier contributory factors in antenatal and intrapartum period.

	Antepartum period		Intrapartum period
	Ante partum stillbirth, n (%) (n = 146)	Intrapartum stillbirth, n (%) (n = 77)	Intrapartum stillbirth, n (%) (n = 77)
Family level			
Reached late or no antenatal care	25 (17.1%)	12 (15.6%)	7 (9.1%)
Cultural inhibition to seeking care	3 (2.1%)	3 (3.9%)	–
No knowledge of danger sign/lack of recognition of seriousness	65 (44.5%)	23 (29.8%)	2 (2.6%)
Non availability of accompanying person	10 (6.8%)	5 (6.5%)	1 (1.3%)
Financial constraints	6 (4.1%)	5 (6.5%)	–
Non compliance	9 (6.2%)	3 (3.9%)	–
Use of home remedies	3 (2.1%)	5 (6.5%)	–
Communication gap	6 (4.1%)	1 (1.3%)	–
Refusal by family for neonatal care/not willing for cesarean for fetal indication	–	–	10 (12.9%)
Others	5 (3.4%)	6 (7.8%)	–
Administrative level			
Non availability of delivery facilities	26 (17.8%)	4 (5.2%)	15 (19.5%)
Lack of training	3 (2.1%)	6 (7.8%)	–
Incomplete or no antenatal case records	4 (2.7%)	1 (1.3%)	–
Insufficient staff	2 (1.4%)	3 (3.9%)	–
Non availability of NNU/NICU	1 (0.7%)	1 (1.3%)	–
Others	1 (0.7%)	1 (1.3%)	–
Provider level			
Delay in referral	20 (13.6%)	10 (12.9%)	–
Inappropriate action taken	35 (23.9%)	15 (19.5%)	–
Inappropriate discharge	–	5 (6.5%)	–
Failure to follow best practices and guidelines	13 (8.9%)	4 (5.2%)	–
Inadequate monitoring/lack of training	5 (3.4%)	1 (1.3%)	3 (3.8%)
Others	6 (4.1%)	2 (2.6%)	–

Table 4: Recommendations made in monthly audits and implemented.

Recommendations which were implemented
– To strengthen obstetrics triage-guidelines were made
– Changes in practice were made by identifying latest evidence after reviewing the literature
– Fetal growth charts for fetal monitoring (intergrowth 21)
– Learning by discussing preventable causes of stillbirths to sensitize the junior doctors.
– To create awareness and get acquainted to integrate into new practices
– Regular feed back to referral centers

Acknowledgments: The data used in this study is also collected for Newborn and Birth Defect Database (NBBD) under WHO SEAR project. The authors would like to acknowledge WHO SEAR team Dr. Neena Raina, Dr. C Anoma Jayathilaka, Dr. Rajesh Mehta, Dr Priya Karna and Mr Dhiraj Kumar for their support and Dr Ashok Kumar, Department of Neurology, National institute of Nursing Education, PGIMER Chandigarh for data analysis.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Ethical approval was obtained from Institutional ethics committee, Postgraduate Institute of Medical Education and Research, Chandigarh, India on 09.04.2019, PGI/IEC/2019/00762 (P-552).

References

1. Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. *Lancet* 2021;398:772–85.
2. Hug L, Mishra A, Lee S, You D, Moran A, Strong KL, et al. A neglected tragedy the global burden of stillbirths: report of the UN inter-agency group for child mortality estimation. New York, USA: UNICEF; 2020.

3. WHO U. Every newborn: an action plan to end preventable deaths. Geneva: World Health Organization; 2014.
4. Kuruvilla S, Bustreo F, Kuo T, Mishra CK, Taylor K, Fogstad H, et al. The Global strategy for women's, children's and adolescents' health (2016–2030): a roadmap based on evidence and country experience. *Bull World Health Organ* 2016;94:398.
5. World Health Organization. Every newborn action plan: progress report; 2015.
6. World Health Organization. Making every baby count: audit and review of stillbirths and neonatal deaths. Geneva, Switzerland: WHO Document Production Services; 2016.
7. Norris T, Manktelow BN, Smith LK, Draper ES. Causes and temporal changes in nationally collected stillbirth audit data in high-resource settings. In: *Seminars in Fetal and Neonatal Medicine*. United Kingdom: WB Saunders; 2017, 22: 118–28 pp.
8. Neonatal–perinatal database and birth defects surveillance report of the regional review meeting, New Delhi, India, 2014. Available from: apps.searo.who.int/PDS_DOCS/B5227.pdf.
9. World Health Organization. The WHO application of ICD-10 to deaths during the perinatal period: ICD-PM. Geneva, Switzerland: World Health Organization Document Production Services; 2016.
10. World Health Organization. The world health report 2006: working together for health. France: World Health Organization; 2006.
11. De Bernis L, Kinney MV, Stones W, ten Hoope-Bender P, Vivio D, Leisher SH, et al. Stillbirths: ending preventable deaths by 2030. *Lancet* 2016;387:703–16.
12. Child EW. Saving lives, protecting futures: progress report on the global strategy for women's and children's health 2010–2015. Italy: Every Woman Every Child; 2015.
13. Tveit JV, Saastad E, Stray-Pedersen B, Børdahl PE, Flenady V, Fretts R, et al. Reduction of late stillbirth with the introduction of fetal movement information and guidelines—a clinical quality improvement. *BMC Pregnancy Childbirth* 2009;9:1–10.
14. Heazell AE, Weir CJ, Stock SJ, Calderwood CJ, Burley SC, Froen JF, et al. Can promoting awareness of fetal movements and focusing interventions reduce fetal mortality? A stepped-wedge cluster randomised trial (AFFIRM). *BMJ Open* 2017;7: e014813.
15. Sovio U, White IR, Dacey A, Pasupathy D, Smith GC. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet* 2015; 386:2089–97.