Epidemiology of Fetal and Neonatal Death

6

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Abstract

Introduction: A perinatal death refers to fetal or neonatal death, combined to calculate the perinatal mortality rate. High perinatal mortality rates indicate unmet public health needs and also deficiencies in clinical care provision. The death of a child around the time of birth has profound effects on parents and families. Increasing attention is being paid to reducing these deaths. Epidemiological analyses aid in the identification and monitoring of prevention strategies.

Objectives: This chapter provides an overview of the epidemiology of fetal and neonatal death globally including numbers, rates, causes, and risk factors and highlights issues that limit the utility of perinatal mortality as a measure of health and quality of care including classification systems to assign causes of perinatal deaths.

Key Points: An estimated 2.9 million neonatal deaths and 2.6 million late gestation stillbirths (after 28 weeks of gestation) occur globally each year. These numbers almost double when using the definitions of stillbirths and neonatal deaths of high-income countries (i.e., from 20 weeks of gestation). The vast majority of these deaths occur in low- and middle-income countries and are avoidable. Since 1990, the global neonatal death rate has decreased by 37 %, from 33 to 21 deaths per 1,000 livebirths; however, this is slower than the 50 % reduction in deaths in the postneonatal period up to the age of 5. The decline in the stillbirth rate has been slower: an estimated 14.5 % reduction from 22.1 to 18.9/1,000 (1995–2009). Wide variation in rates exists within and across countries. The majority of deaths occur in the 24 h around the time of birth, where increased access to quality obstetric and newborn care could halve these deaths. The lack of data on numbers and causes of death plagues prevention efforts. Further, the use of numerous disparate classification systems makes interpretation of causes of perinatal deaths difficult. However, placental pathology (including abruption and insufficiency) often associated with growth restriction is clearly a major contributor to stillbirth globally, in addition to low-income settings, hypertensive disorders, and infection in some regions. The proportion of unexplained stillbirth varies widely across reported studies. The causes of neonatal deaths have been more consistently reported and are largely due to complications of preterm birth, intrapartum-related events, and infections. Intrapartum factors have been reported as causal in 40 % of perinatal deaths in low-income country settings. Women living in disadvantage have much higher rates of stillbirths and neonatal deaths than their counterparts. Clinical audits consistently show that a high proportion of perinatal deaths are potentially avoidable.

Conclusions: Stillbirth and neonatal death rates are widely used as an indicator of the health of communities and the quality and safety of obstetric and newborn care. While low- and

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middle-income countries bear the majority of the burden, slow progress in reducing neonatal deaths and, more prominently, stillbirths is a worldwide problem. Improvements in the living standards for disadvantaged women, including education and employment opportunities and access to quality care, are imperative to address the disparity in outcomes across all settings. Epidemiological methods applied to perinatal data can assist in understanding where to focus attention. However, the paucity of high-quality data limits such analyses, posing a significant challenge to prevention of perinatal deaths. More effective data systems are needed, including a global classification system.

Keywords

Epidemiology • Fetal death • Stillbirth • Neonatal • Perinatal • Mortality • Classification • Risk factors

The perinatal period (commonly defined as the phase surrounding the time of birth, from the 20th week of gestation to the 28th day of newborn life) [1] is the most vulnerable period in the life. The risk of dying on the day of birth exceeds that of any other average day of life until the 92nd year [2].

A perinatal death refers to fetal or neonatal death, combined to calculate the perinatal mortality rate (PMR). While the term "fetal death" is most accurate, the term "stillbirth" is preferred by parents and the community [3]; the terms are often used synonymously. The death of a child around the time of birth is highly contradictive to the "natural order" of life and has profound effects on parents and families, which often suffer significant disruption to relationships and substantial economic burden [4].

According to the World Health Organization (WHO), the perinatal mortality rate provides a "general measure of the health environment during the earliest stages of life" and can also be used as "a measure of action in relation to health policy and health service interventions" [5].

This chapter provides an overview of the epidemiology of fetal and neonatal death. It presents rates, causes, and risk factors and also a summary of contemporary classification systems to assign causes of perinatal deaths. While stillbirth and neonatal death are both closely linked with maternal health [6], important etiologic differences exist and successful preventive efforts must draw on specific data for each of these two groups. The stillbirth rate reflects the general health of women and the quality of obstetric care, and while this is also true for neonatal deaths, neonatal practices play a critical role in the survival of newborns [6]. Therefore, in this chapter, stillbirth and neonatal death will be presented separately where data permit.

Definitions

Stillbirth is defined by WHO as "death prior to the complete expulsion or extraction from its mother of a product of conception…the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles." A birthweight of 500 g or more, 22 or more completed weeks of gestation, or a body length of 25 cm or more is used to define stillbirth. For international comparisons, WHO recommends reporting of stillbirths with birthweight of 1,000 g or more, 28 weeks of gestation or more, or a body length of 35 cm or more. A number of high-income countries (HIC) use a lower gestational age and birthweight cutoff. The stillbirth rate is expressed as the number of stillbirths per 1,000 births.

Neonatal death is the death of a live born baby within the first 28 days of life. It can also be divided into: early neonatal death within the first 7 days of life and late neonatal death after 7 days until 28th day of life. The neonatal mortality rate is the number of deaths per 1,000 live births (Fig. 6.1).

Perinatal mortality refers to stillbirth plus *early* neonatal deaths (deaths at 7 days or less). The perinatal mortality rate is the number of stillbirths plus early neonatal deaths per 1,000 births. This rate is especially useful in settings where it may be difficult to distinguish a late stillbirth from an early neonatal death. The definition of neonatal death includes deaths up to 28 days of life in HIC and also some of the lower-income countries.

Data Quality Issues

Definitions for stillbirth, perinatal, and neonatal data vary widely. Even among HIC, at least 20 different definitions have been reported recently [8]. Differences in application of gestational age and birthweight cutoffs are a common source of this variation. Birthweight is often prioritized over gestational age in defining stillbirth because it is more widely available, especially in low-resource settings, and reliably reported. However, this may result in substantial underreporting of stillbirths [9]. In low- and middle-income countries (LMIC), whether early neonatal deaths alone or both late and early neonatal deaths are reported varies depending

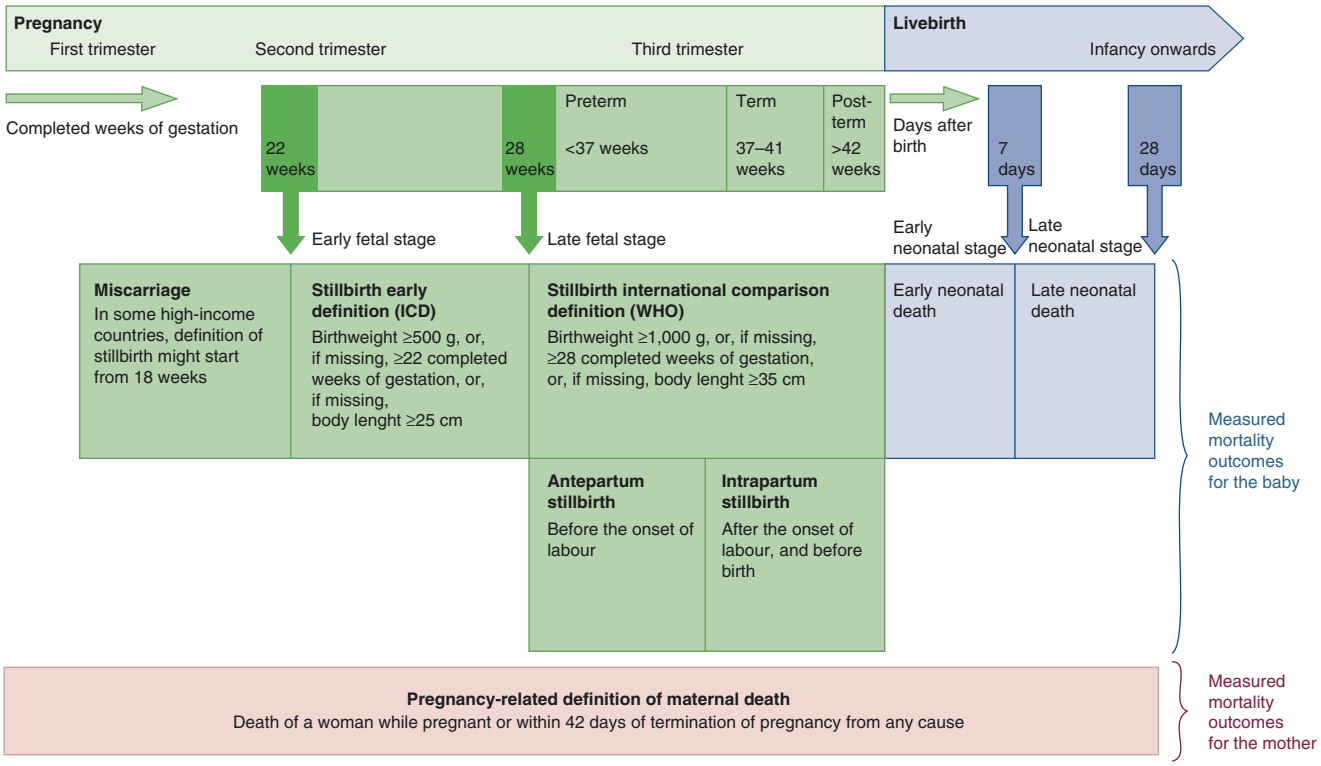


Fig. 6.1 Defining stillbirth and neonatal death. Defining stillbirths, neonatal deaths, and associated pregnancy outcomes for international comparison. Definitions from ICD, tenth revision. *ICD* International Classification of Diseases (Reprinted by permission from Lawn et al. [7])

on data availability. Additionally, misclassification of early neonatal deaths as stillbirths is an important issue that is closely linked to practices and perceptions around viability and the obstetric care available within some settings. Finally, the different practices for inclusion of medical terminations of pregnancy also may result in important variation in perinatal mortality rates.

While vital statistics are generally a good source of births and deaths in HIC, 40 % of the world's births do not have a birth certificate and around one-third are in regions with inadequate vital registration coverage. In such settings, estimates of numbers and rates are modeled based on surveys such as national census and household surveys [10, 11]. Due to limited resources, surveys are infrequently conducted (every 5–10 years), and with the added problem of recall bias, these data are extremely limiting for identifying areas for prevention. Depending on the level of missing data, confidence intervals can vary widely. For example, the stillbirth rate estimate for Afghanistan is 24.9 per 1,000 total births, giving 38,000 stillbirths with a range from 24,000 to 72,000 [11].

Due to the often complex nature of perinatal deaths, accurate ascertainment of cause and contributing factors of perinatal deaths is best achieved by perinatal audit committees made up of clinical experts following detailed investigation of the death [12]. However, in many regions of the world, this is not possible and death certificate data are relied upon. However, these data are notoriously inaccurate [13]. For example, the Australian Bureau of Statistics reports stillbirth as "undetermined" in up to 70 % of stillbirths [14], whereas following comprehensive investigation and review by audit committees, this proportion may be reduced by 65 % [15]. While training of clinicians in completion of death certificates may improve the quality of these data, the inherent issue of lack of information about the case at the time of completion of death certificates will always limit their value for perinatal deaths. Additionally, in some LMIC settings, death certificates are required for live births but not stillbirths, an important gap in information.

High-quality investigation including autopsy and placental histopathology is important in accurately determining the cause of perinatal deaths. In HIC, while placental pathology is generally regularly performed, autopsy rates are variable and low rates of 30–40 % are commonplace. Barriers to autopsy consent have been addressed in detail elsewhere (Chap. 1). However, in HIC these would appear to be largely surmountable as evidenced by some regions achieving a rate of 70 % or more. In low-resource settings, access to such diagnostics is often not possible. To establish the cause of perinatal deaths in community-based settings in low-income country (LIC) settings, verbal autopsies (VA) (which are interviews with either caregivers or family of the deceased) have been used [10]. Furthermore, the lack of a skilled birth attendant at delivery often means the most basic information

Table 6.1 Advantages and disadvantages of different data sources for studies of perinatal mortality

	Advantages	Disadvantages
National statistics *routine data collections*	Large numbers	Limited amount of information. Cause of death data largely meaningless (as described in the next section). Possible under-ascertainment of deaths. Lack of quality control on information
National surveys *using data specially collected over a defined period of time*	Improved quality of data. Ability to classify deaths in a standard way. Large amount of information available for analysis	Relatively small numbers of deaths unless the sample is extended, as in the First British Perinatal Mortality Survey [26] or the Jamaican study [27]
Ongoing area-based maternity information	Quality control is possible, especially if organized so that research clerks abstract the information using well-formulated rules, with referral to consultant medical staff in cases of difficulty	High cost; relatively small numbers
Hospital-based statistics	As above	As in above. In addition, the data are epidemiologically uninterpretable unless the hospital serves the whole of a geographical population. Otherwise it is essential to ascertain also the outcome of pregnancy in all women resident in the referral area but delivered outside the hospital
Prospective studies	Surveys starting in pregnancy or even before have the benefit of greater accuracy in determining features relating to the mother and the pregnancy prior to the death occurring	High cost; relatively small numbers

Adapted from Chapter 9 Jean Golding *Keeling's Fetal and Neonatal Pathology 4th Edition* [18]

is not available (e.g., weight or gestation), so establishing cause of death remains problematic.

Epidemiological Principles and Challenges in Perinatal Mortality

Epidemiology is the science that studies the patterns, causes, and effects of health and disease conditions in defined populations. Epidemiological (observational) studies are the cornerstone of public health and inform policy decisions and evidence-based practice largely by identifying risk factors for disease and targets for preventive healthcare [16]. While observational studies will generally yield only low-quality evidence, extremely large and consistent estimates of the magnitude of an effect increase confidence about the results [17].

Satisfactory analyses of perinatal data require a clear understanding of what is being measured, whether the comparisons are valid (comparing like with like) and if the conclusion takes into account the limitations of the data [18]. Often perinatal mortality is compared across health services to assess the quality of care. However, the difficulty of adequately controlling for differences in population characteristics (often due to referral patterns) is problematic. When interpreting results of such analyses, a careful look at the factors that were considered as potential confounders and the possible effect of "residual confounding" is essential. The public health burden of a risk factor to stillbirths and neonatal deaths is often quantified using the population attributable fraction/risk (PAF/PAR), the proportional reduction in these deaths that would occur if exposure to a risk factor were removed.

Capturing data on associated risk factors such as geographical location and socioeconomic status, to allow disaggregation of perinatal mortality data, enables programs to improve resource allocation and monitoring [19]. Perinatal mortality rates are often presented using time trends and may incorporate quasi-experimental before-and-after study designs and/or time series analyses to examine whether an intervention demonstrated benefit. The problem is that many factors change over time including characteristics of the population and other practices and these need to be taken into account.

There are a number of methods of data capture for perinatal mortality studies each with advantages and disadvantages. Demographic surveillance (the process of continuous registration of demographic events, in a geographically defined population) is used to enable more in-depth analyses. An example is the INDEPTH network, the largest network of demographic surveillance sites, mainly in Africa, monitoring people at household level [20]. Some countries have implemented large-scale clinical audit programs in perinatal mortality to more effectively "close the audit loop," e.g., South Africa [21], the UK [22], the Netherlands [23], and New

Zealand [24]. Other initiatives aimed at upscaling effective perinatal audit and practice improvement through criterion-based data collection systems are emerging [25]. Advantages and disadvantages of commonly used approaches were previously described by Jean Golding and are summarized in Table 6.1 [18].

Numbers, Rates, and Trends

Recent papers from Lawn et al. [6, 7] provided a comprehensive summary of the global stillbirth and neonatal death. The key epidemiological aspects of these papers are summarized in this section of the chapter.

The most recent global estimates show that the neonatal death rate is 21/1,000 and the stillbirth rate (after 28 weeks of gestation) is 18.9/1,000. These rates equate to around 2.9 million neonatal deaths and 2.6 million late gestation stillbirths (after 28 weeks of gestation) each year [6]. However, these numbers are likely to be a gross underestimate. The uncertainty range for stillbirth estimates indicates that up to 3.8 million stillbirths may occur annually, and applying the definition used across most HIC settings, the figure could reach over 6 million.

The vast majority of stillbirths and neonatal deaths (over 98 %) occur in LMIC and almost half occur during labor or shortly after the birth [6]. More than 60 % of neonatal deaths occur across five countries: India, Nigeria, Pakistan, China, and Democratic Republic of Congo. These countries also account for the majority of stillbirths and maternal deaths (Fig. 6.2). Almost one-half of stillbirths occur intrapartum (after the onset of labor). More than 70 % of all neonatal deaths occur during the first week of life, with almost 40 % on the day of birth [6].

Wide variation in rates exists across and within countries for both late gestation stillbirth and neonatal death rates. Late gestation stillbirth rates vary from 2/1,000 births in Finland to more than 40/1,000 total births in Nigeria and Pakistan [6]. The neonatal death rate ranges from 1/1,000 in Japan to 49/1,000 in Sierra Leone [6].

In HIC, the neonatal death rates are around 3–4/1,000 livebirths [28, 29]. Due to varying definitions, stillbirth rates are difficult to compare across HIC. In the USA [29] and Australia [28], which use similar definitions (from 20 weeks), stillbirth rates are 6.1 and 7.8/1,000 births respectively. Even when using the WHO definition of late gestation stillbirth, significant variation in rates can be seen across HIC suggesting that further improvement is possible and needed [30] (Fig. 6.3). For example, in 2009, the late gestation stillbirth rate was 2/1,000 in Finland and Singapore compared with 3.5/100 in the UK [7]. Indigenous women and others living in disadvantage in HIC have around double the rates of stillbirth and neonatal deaths as their counterparts [24, 31].

Are Stillbirth and Neonatal Death Rates Improving?

As observed through the United Nations' Millennium Development Goal (MDG) 4 to reduce child death and MDG5 to reduce maternal deaths, the health of women and children has clearly improved. From 1990 to 2012, the annual rate reduction for maternal deaths was 2.6 % and under five child mortality 3.4 %. However, the reduction in neonatal deaths has been much slower (2.0 %) and slower again for stillbirths (1.0 %) [6]. This is especially true for LMIC, which have shown only minimal reductions in some countries.

In HIC, with marked reductions in perinatal mortality rates seen in the early 1940s and 1950s, stillbirth now makes up the majority (around 70 %) of perinatal deaths with the majority of deaths (90 %) occurring in utero before the onset of labor. While neonatal death rates have continued to decline slowly in HIC [28, 29], stillbirth rates have shown little or no reduction over recent times [29]. Recent data from Australia has shown an increase in overall stillbirth rates, which is confined to the lower gestational age groups (<25 weeks) [28]. Others have shown that increases in stillbirth rates in HIC are due to increases in termination of pregnancy with associated reductions of live births with congenital abnormalities [32]. The rates of stillbirth for indigenous women in Australia have shown some improvement over recent times [31], but the gap between indigenous and non-indigenous women remains wide. Despite the low rates in comparison to LMIC, stillbirth remains a significant public health problem in these settings, exceeding deaths from sudden infant death syndrome (SIDS) by a factor of 10, but receiving much less public health attention.

Classification of Stillbirth and Neonatal Death

Accurate and consistent classification of cause and major contributing factors for stillbirth and neonatal death is the cornerstone of effective prevention strategies to reduce these deaths. According to Whitfield, the goal of classification of perinatal deaths is "to identify deficiencies in the provision of care, to focus attention where improvements are already possible and to indicate where new developments or knowledge may be expected to lead to further advances" [33]. Suboptimal classification systems may lead to a loss of important information and contribute to a high proportion of unexplained deaths [34], thereby diminishing the potential for prevention. Due to inadequacies of the WHO International Classification of Disease (ICD) system for both stillbirth and neonatal deaths, clinicians and researchers have been considering ways of classifying these deaths for more than two decades [35]. More than 35 systems have reportedly been

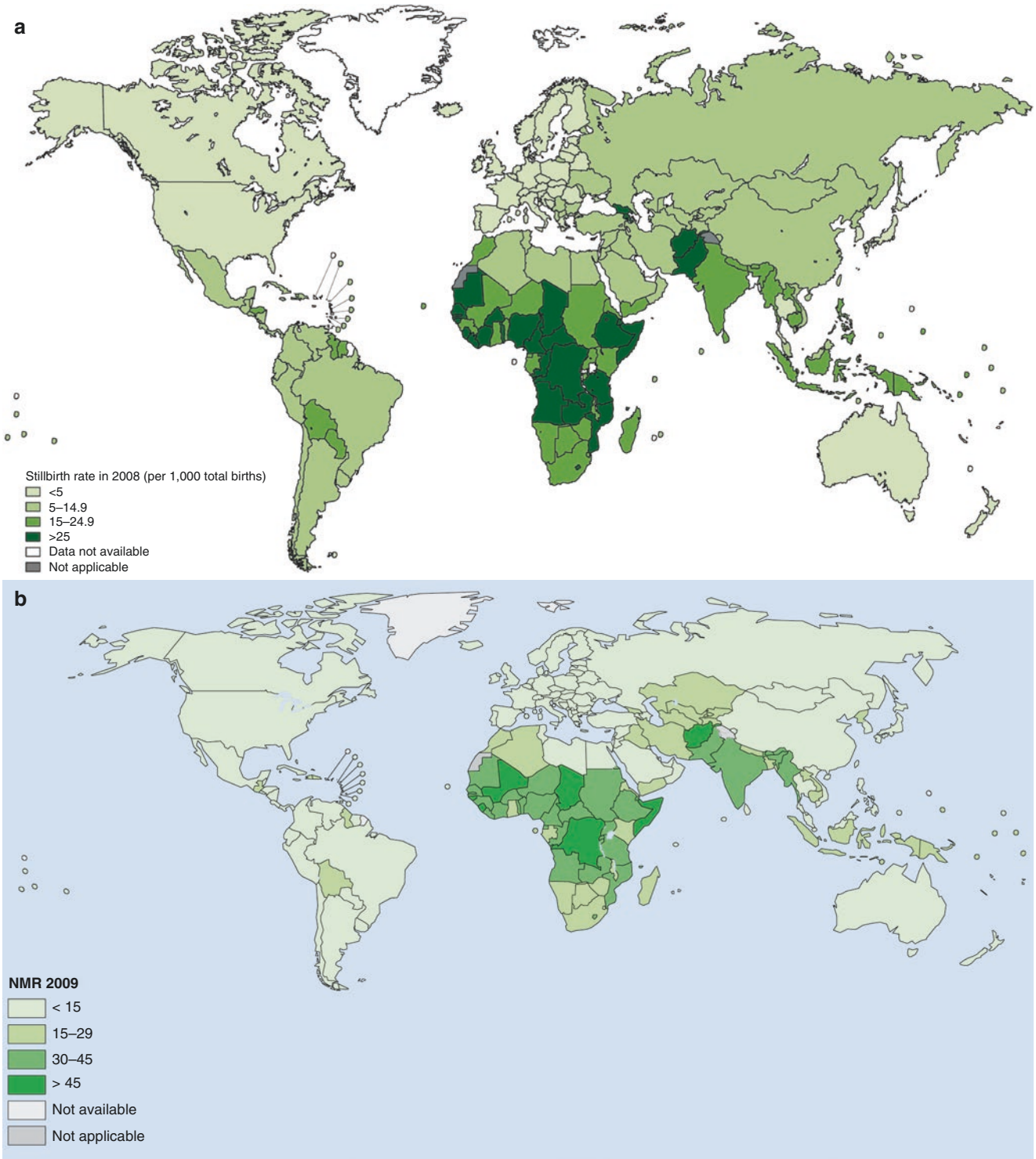


Fig. 6.2 Stillbirth and neonatal death rates by country. (**a**) Stillbirth rates by country in 2009 (Reprinted by permission from Lawn et al. [7]). (**b**) Neonatal death rates by country in 2009 (Reprinted from http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001080# © 2011 World Health Organization; licensee Public Library of Science (PLoS)). This is an open access article in the spirit of the Public Library of Science (PLoS) principles for open access http://www.plos.org/oa/, without any waiver of WHO's privileges and immunities under international law, convention, or agreement

developed for stillbirth and perinatal mortality alone [36]. A recent review of systems in current use revealed that the number of new or major modifications of systems has increased over the past decade [8]. The use of disparate systems renders meaningful comparisons across and within countries virtually impossible. The most commonly reported

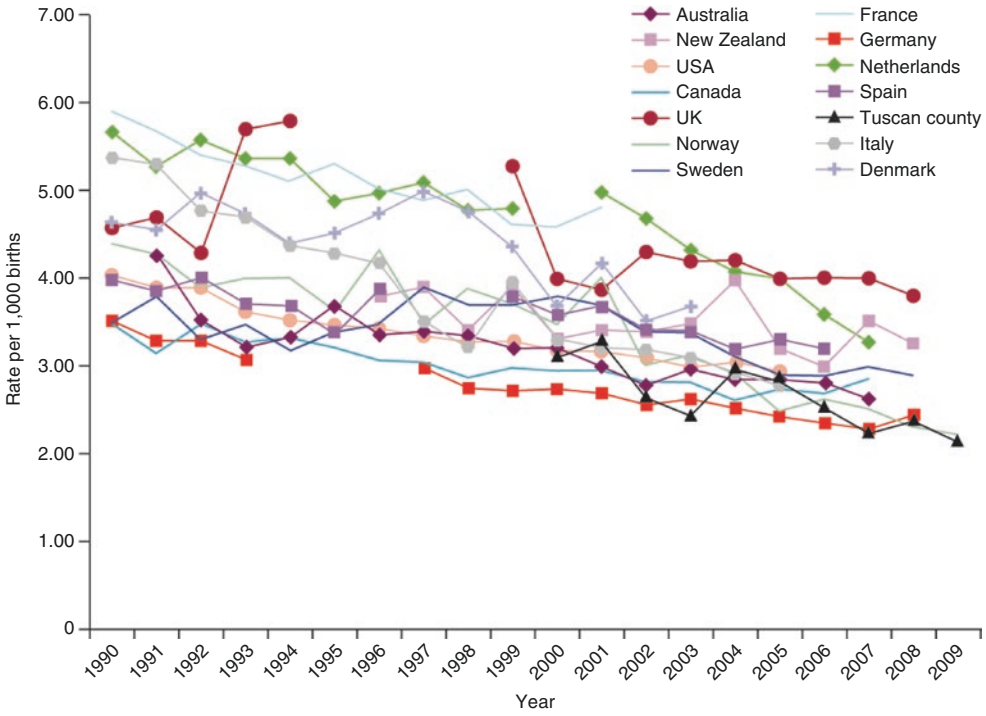


Fig. 6.3 Stillbirth rates (28 weeks or more of gestation) in selected high-income countries 1990–2008/2009 (Reprinted by permission from Flenady et al. [30])

and recently published new systems (since 2009) are briefly summarized here:

Many contemporary systems are based on those developed in the UK and subsequent modifications throughout the mid to late 1900s. Of note is the clinicopathological system developed by Sir Dugald Baird and colleagues in Aberdeen [37], which focused on maternal/obstetric antecedent conditions "to classify each death in accordance with the factor which probably initiated the train of events ending in death." The other major system in this period was developed by Wigglesworth [33]: a simple five-category pathophysiological classification system for perinatal deaths developed to provide more information on causes of neonatal deaths [33]. The Wigglesworth classification [33] is one of the most widely used systems for classifying perinatal deaths, particularly in LMIC [38–46].

Baird et al., using the Aberdeen system, showed the following distribution of causes of a series of perinatal deaths at Aberdeen Maternity Hospital in 1938–1952 as: premature (<5 1/2 lb), cause unknown (20 %); mature, cause unknown (14 %); trauma, mechanical stress during labor (19 %); toxemia (10 %); antepartum hemorrhage (11 %); maternal disease (6 %); fetal deformity (15 %); and other causes (5 %). A later modification by Cole et al. (Amended Aberdeen) [47] included categories of serological incompatibility, infection of the fetus or infant, and unclassified (where information was inadequate). Subsequently, Whitfield et al. in 1986 [48] amended this into a new 12-category system for stillbirths, neonatal deaths, and postneonatal deaths that were prenatally related, defining categories of unexplained intrauterine death and fetal growth restriction groups (intrauterine growth retardation) and inclusion of spontaneous preterm, hemolytic disease, and infection groups and also differentiating intrapartum asphyxia from birth trauma. More recently, recognizing the contribution of placental pathology in perinatal death, the National Services Scotland further refined the obstetric antecedent approach to include a category of specific placental pathology including eight subcategories [49].

Hey et al., in 1986, expanded on the Wigglesworth system to develop fetal and neonatal factor classification [50] and also a six-group Wigglesworth classification, adding an "unclassified" group. The fetal and neonatal factor classification was further developed to suit the modern neonatal care settings in Australia and New Zealand, by Ross Haslam et al. of the PSANZ [35] with subsequent amendments [12].

In LMIC settings, the most widely used system reporting comprehensive global data on causes of neonatal deaths is the simple five-category system refined by the Child Health Epidemiology Reference Group (CHERG) [51, 52].

In 1998, Winbo et al. developed the Neonatal and Intrauterine Death Classification according to Etiology (NICE) system [53] for stillbirths and neonatal deaths based on the Amended Aberdeen and Wigglesworth systems. This system was originally designed to identify the underlying cause of perinatal death using a computer algorithm applied to registry data as a solution to exhaustive work required by expert panels to review case notes to assign cause of death. Recently, using the verbal autopsy approach [54], the NICE system [53] has been used to classify stillbirths [10, 55, 56] and also in combination with CHERG [51] to identify causes of stillbirth and neonatal deaths [57].

The use of an obstetric antecedent classification for stillbirths and neonatal deaths and, in addition for neonatal deaths, a neonatal system to identify a "final cause of neonatal death" [58] based on systems developed more than three decades ago is a common approach today. Systems using the approach include: Problem Identification Programme (PPIP) used nationally in South Africa [21], Pakistan [59], and a multicountry study in LMIC [60]; the Perinatal Society of Australia and New Zealand (PSANZ) classification system [12] used nationally in Australia and New Zealand and regionally in Canada; Centre for Maternal and Child Health Enquiries (CMACE) in the UK [22]; and the Scottish Obstetric and Paediatric classification [61].

A number of new systems have emerged over recent times with more detailed categories and a greater focus on placental pathology including: the Stockholm classification of stillbirth [62] currently used across the Stockholm region; INCODE (Initial Causes of Fetal Death) [63] classification for stillbirths developed specifically for the Stillbirth Collaborative Research Network (SCRN) of the National Institutes of Child Health and Human Development (NICHD); Tulip for perinatal deaths [64] developed and used in a network of hospitals across the Netherlands; and Codac (Causes of death and associated conditions) [9] for stillbirths and neonatal deaths, which uses an electronic tool to aid classification and recently implemented for national audit in the UK [65]. The ReCoDe (relevant condition at death) system [66] used in regions in the UK, and also in some centers in LMIC settings, aims to identify relevant conditions for stillbirth as opposed to causes and thereby reducing the requirement for laboratory evidence. Other published systems include that used by the Wisconsin Stillbirth Service Program (WiSSP) [67] (a referral program to define causes of stillbirth using a comprehensive protocol focusing on congenital abnormalities).

Important Features of a Good Classification System

A recent Delphi study of experts identified characteristics of a quality global perinatal classification system [8] to assist in identifying a system that may be suitable as a global solution. However, a review of systems in use since 1995 revealed that no individual system met these characteristics [8]. The major characteristics are discussed here and summarized in Table 6.2 [7, 9, 22, 26, 33, 35, 37, 47, 48, 50, 51, 53, 57, 62–64, 66–72].

While it is important to analyze the causes of perinatal death according to its components of stillbirth and neonatal death [73], a system specifically designed to incorporate both groups enables interpretation of differences across regions arising from variation in definition, reporting, and registration practices for perinatal deaths. Many systems in current use either have a focus on obstetric (maternal/fetal conditions) (for use in both stillbirths and neonatal deaths) or neonatal conditions only. Some use these two approaches in tandem. However, this can be cumbersome and challenging to interpret.

The value of any death classification system is closely aligned with its ability to identify the underlying cause of death but also to retain important information relating to the death. To identify specific areas to focus prevention, identifying an underlying cause is needed. ICD-10 defines the underlying cause as "the disease or condition that triggered the chain of events leading to the death." However, assigning a single cause is often challenging due to the complexity of the clinical situation within which the fetus, and often also the newborn, dies [33]. The presence of certain conditions commonly represents a continuum of risk of stillbirth from weak to convincing evidence of a causal link. Take the example of a cord complication and a late gestation stillbirth at one end of the spectrum to limb entanglement, congestion, and fetal thrombotic vasculopathy in the placenta at the other (Fig. 6.4 [74]).

To assist users in assigning an underlying cause, and to enhance validity of cause of death data, instructions and rules are required. Some systems employ a strict hierarchy [53, 66] where a primary condition is assigned according to the order in the list of categories, those higher up the list taking precedence. This approach is believed to also enhance ease of use of the system, particularly when competing conditions are present. However, others [9] debate that application of a strict hierarchy results in erroneous data in some circumstances, due to forced classification of less important factors that are listed higher up [75]. Some systems use a partial hierarchical approach classifying terminations of pregnancy [9] and major congenital abnormalities [35] above other conditions as a rule. The ReCoDe system includes the category of fetal growth restriction (FGR) high up in the hierarchy. In a recent study, Ego et al. [75] showed that by modifying the ReCoDe hierarchy by making the FGR category, the penultimate category changed the proportion of stillbirths classified as FGR from 38 % to 14 %, in favor of other related conditions. While ReCoDe does not follow the rules for underlying cause [76], it does enable cross tabulation with associated factors to gain further information as to the etiology of the FGR.

The utility of classification systems lies in the extent to which useful information about the death is conserved [9]. In one study, testing six contemporary systems across seven countries (including two LMIC), the Wigglesworth and Amended Aberdeen systems scored lower than the other systems in the ability to retain important information about stillbirth. Codac received the highest score followed by PSANZ-PDC and ReCoDe and then Tulip. Wigglesworth

Table 6.2 Characteristics of major contemporary classification systems for stillbirth and neonatal deaths

Name of system	Intended for stillbirth and neonatal deaths, and are distinguishable?	Modified from	Number of categories per level	Uses ICD codes	Country developed	Countries using system to determine causes of death
Aberdeen [37]	No perinatal deaths	n/a	8	No	UK-Scotland	Nigeria
Amended (modified) Aberdeen [47]	No perinatal deaths	Aberdeen (as per Baird and Thomson 1969 modification) [69]	10/19	No	UK	Northern Ireland, Netherlands, UK Pakistan with further modifications
Wigglesworth [33]	No perinatal deaths	n/a	5 (some use 6 categories adding "unclassifiable)	No	UK	UK. Nepal, Nigeria, Pakistan, Bangladesh, Ireland, Turkey, Thailand
ICE (International Collaborative Effort) [70]	No perinatal deaths	Wigglesworth	8	Yes	UK-Scotland	Tanzania, USA, Canada, Scotland with modifications expanding the categories
Fetal and Neonatal Factors (F&NF) [50]	No perinatal deaths	Based on the Butler and Bonham [26] Aberdeen amendments and Wigglesworth	11/18	No	UK	Belgium, Northern Ireland, Brazil, UK
Perinatal Problems Identification Program (PPIP) Obstetric and Neonatal 2012	Partially through use of tandem systems	O: Aberdeen Whitfield [48] amendment N: F&NF Plus early versions of PPIP from 1990s	O: 12/68 N: 7/50	"Based in ICD"	South Africa	South Africa (national) NICHD research network across LIC communities, Pakistan
Perinatal Society of Australia and New Zealand Perinatal Death (PSANZ-PDC)/Neonatal Death Classification (PSANZ-NDC)	Partially through use of tandem systems	O: Aberdeen Whitfield [48] amendment Chan [35] N: F&NF, Chan 2004	O: 7/37/28/23 N: 11/67/62	No	Australia and New Zealand	PSANZ-PDC Australia, New Zealand (national), Vietnam PSANZ-NDC Canada
CMACE Maternal and Fetal and Neonatal Classifications 2008 [22]	Partially through use of tandem systems	O: CESDI Northern Ireland 2001 [71] (from Aberdeen and Wigglesworth) N: F&NF	O:13/20 N: 10/10	No	UK	UK, also used in Pakistan with modifications
Scottish Obstetric and Pediatric Classification 2011 National Services [72]	Partially through use of tandem systems	O: Amended Aberdeen CESDI N: F&N Factors	O: 11/26; N: 9/25	Yes	UK-Scotland	UK-Scotland
Manandhar [57]	Partially through use of tandem systems	O: NICE with VA rules by Anker et al. 1999 N: CHERG	O: 7 N: 7	No	Nepal	Nepal
NICE (Neonatal and Intrauterine Death Classification according to Etiology) [53]	Partially: includes a category for neonatal conditions	n/a	13	Yes	Sweden	India, Tanzania, Pakistan, Nepal; modified and used with verbal autopsy data in these LMIC

(continued)

Table 6.2 (continued)

Name of system	Intended for stillbirth and neonatal deaths, and are distinguishable?	Modified from	Number of categories per level	Uses ICD codes	Country developed	Countries using system to determine causes of death
ReCoDe (Relevant Condition at Death) [66]	No stillbirths	n/a	9/37	No	UK	UK, Italy, Moldova, Portugal, Nigeria Tested in France using a different hierarchies for FGR
Tulip [64]	No perinatal deaths	n/a	6/30/12	No	Netherlands	Netherlands
Stockholm classification of stillbirth 2008 [62]	No stillbirths	n/a	17/8	No	Sweden	Sweden
Codac (Causes of death and associated conditions) [9]	Yes	n/a	10/94/577	Yes	Norway	Norway; 2014 MBRRACE-UK
INCODE (Initial Causes of Fetal Death) [63]	No stillbirths	n/a	7/46/143/30	No	USA	US research network
Child Health Epidemiology Reference Group (CHERG) 2009 [51]	No neonatal deaths	Bangladesh Demographic and Health Survey 2004; VA approaches [68] NICE and Wigglesworth	7	No	International	Global estimates with modifications by Black et al. and others. Used with VA data in Uganda, Vietnam, Nepal, Burkina Faso with modifications. Bangladesh national reports continue to use similar system
WiSSP Wisconsin Stillbirth Service 2011 [67]	No stillbirths	WiSSP 1994 [9]	6/52 specific causes presented	No	USA	USA –regional referral
Consistent classification for causes of stillbirth [7]	No stillbirths	n/a	3/15	Yes	n/a	Used to present a global picture of causes in *The Lancet*'s stillbirth series

Tandem systems: Use of an obstetric antecedent and, in addition for neonatal deaths, a neonatal system to identify the final causes of neonatal death
O obstetric antecedent classification, *N* neonatal classification, *MBRRACE* Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries, www.npeu.ox.ac.uk/mbrrace-uk, *CESDI* Confidential Enquiry into Stillbirths and Deaths in Infancy, *CMACE* Centre for Maternal and Child Enquiries, *VA* verbal autopsy

and Aberdeen also resulted in a higher proportion of unexplained stillbirths (44 % and 50 %, respectively). In this study, important information sources differed significantly by setting—a factor of the level of investigation performed—e.g., no autopsies were performed in the LMIC group. Maternal and also fetal history was the most frequently reported source of important information in both settings, highlighting the importance of this fundamental part of the investigation protocol. Placental histology and perinatal postmortem examination were important sources of information, consistent with findings of others [34] (Fig. 6.5).

Inclusion of a placental category in a classification system is essential. While some argue that in less well-resourced settings, a placental category is not appropriate due to lack of the availability of histopathology services, using a clinically oriented system in South Africa, Robert Pattinson reported that placenta/placental bed pathology accounted for 23 % of perinatal deaths by combining the categories of placental abruption, preeclampsia, and eclampsia, thus showing that a placental category is relevant to non-HIC settings [77].

A system should result in a low proportion of cases classified as "other" and unexplained cases. However, a system

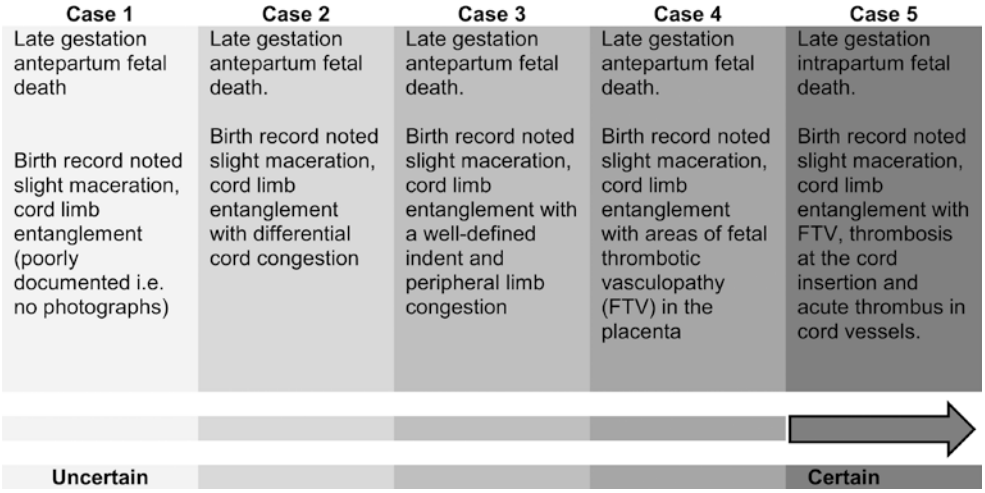


Fig. 6.4 The continuum of risk for conditions implicated in stillbirth (Adapted from Reddy et al. [74]. Scenario courtesy of Dr. Rohan Lourie, Mater Research Institute, University of Queensland, Brisbane Australia)

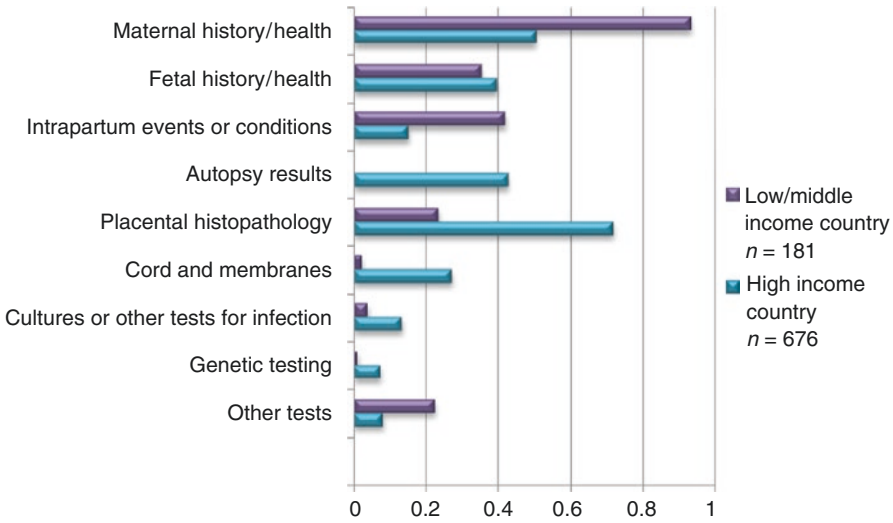


Fig. 6.5 Information sources for classification of stillbirths, by country setting (Adapted from Flenady et al. [34])

that classifies associated conditions as causal factors, to reduce the proportion of unexplained, is also limiting. Unexplained death must be differentiated from those cases where insufficient information was available to enable classification. A definition of unexplained stillbirth has been proposed for only cases that have been fully investigated (i.e., autopsy, placental pathology) [9], but this has not been adopted. The reported proportion of unexplained stillbirths varies widely across systems and is dependent on alternate categories to classify unexplained cases. Korteweg et al. [78], in a review of eight systems, reported that one system [50] had no stillbirths classified as "unclassifiable" or "unknown"; however, 88 % were classified as "asphyxia antepartum," which is not a cause of death but a clinical condition due to an underlying cause of death. Similarly, while the use of ReCoDe [66] results in a low proportion of "unclassified" stillbirths (15 %), as many as 40 % are classified as "fetal growth restriction," thus limiting the opportunity for identifying the underlying cause of the growth restriction. Systems acknowledging the contribution of placental pathology result in lower proportion of unexplained death, e.g., Tulip, Codac, and the Stockholm system. The level of investigation also contributes to proportion of cases that remain unexplained. An understanding of the level of data used to assign the causes of death for each case is helpful to interpret the reported causes of death and also assists in identify areas for practice improvement in investigation of these deaths. Some systems clearly identify where insufficient information is available to assign a cause using an "unclassifiable" category [9] and some systems come part way to this requirement by including the level of certainty, e.g., probable and possible causes [62, 63].

A classification system must produce valid data and therefore reliability (good inter- and intra-rater agreement) is critical. Unfortunately, there is a lack of high-quality studies testing systems. However, in one study, the Aberdeen and Wigglesworth classifications, when applied to stillbirths, showed poor inter-rater agreement (kappas of 0.35 and 0.25, respectively) [34]. In this study, Tulip performed best with a kappa of 0.74 indicating good agreement, and PSANZ-

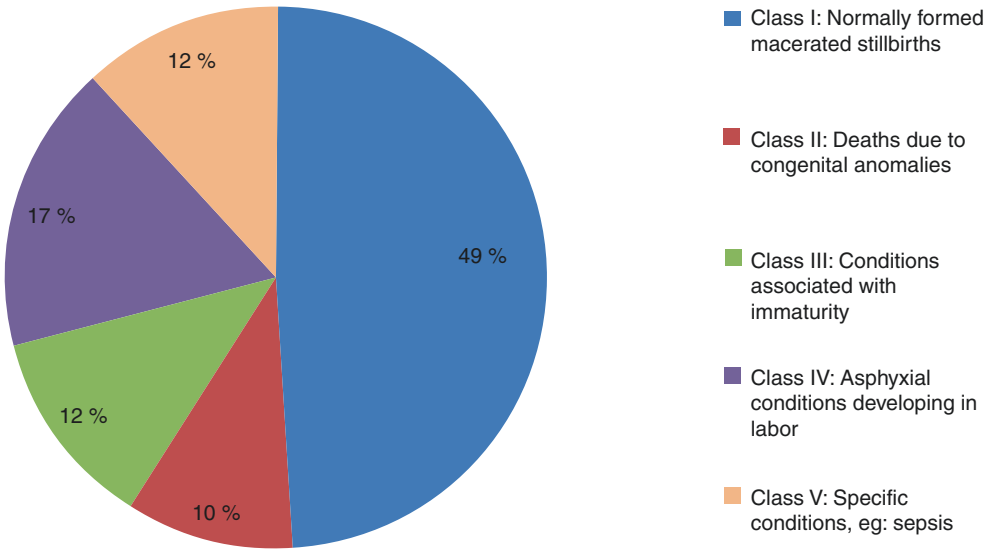


Fig. 6.6 Reported causes of perinatal deaths in a teaching hospital in Nepal, according to Wigglesworth, $n = 921$ (Adapted from Shrestha et al. [79])

Perinatal Death Classification (PDC), Codac, and ReCoDe had fair to good agreement. The Wigglesworth system, applied to perinatal deaths, has been shown to have good agreement in LMIC settings. Efforts to improve agreement in classifying stillbirths and neonatal deaths are needed.

In order to reduce the global burden of stillbirth and neonatal death, classification systems must be suitable for use in LMIC where information is often very limited and major causes of death may vary from those in HIC. However, very few systems have been created specifically for use in LMIC settings. While Wigglesworth has been the most commonly used system in LMIC, testing has shown it to be inferior to other systems for classifying stillbirths [34]. CHERG was developed specifically to accommodate neonatal deaths in LMIC, and, while developed in HIC, ReCoDe [66] and Codac [9] were designed to accommodate stillbirths and perinatal deaths, respectively, in LMIC as well as HIC.

Causes of Stillbirth and Neonatal Death

With numerous disparate systems and poor-quality input data, gaining an accurate global picture of causes of stillbirth and neonatal death is not currently possible. A selection of recently reported studies is presented here to gain some understanding of the commonly reported conditions.

Causes of Perinatal Deaths in Low-Income Settings

In low-resource settings, examining perinatal death, which may have common pathways, has been one approach. For example, one study in a teaching hospital in Nepal using Wigglesworth system highlights the information that can be obtained using a very simple system [79]. In this study of 921 perinatal deaths, the distribution across the five categories were: normally formed macerated stillbirth (i.e., presumed antepartum) 49 %, congenital abnormality 10 %, conditions associated with immaturity 12 %, asphyxial conditions developing in labor 17 %, and other specific conditions (e.g., sepsis) 12 %. While helpful, the lack of specificity of these categories limits focused strategies to prevent these deaths (Fig. 6.6 [79]).

Causes of Stillbirth

This section presents the findings of reports over the period 2009–2014 including the largest population-based studies (or hospital-based reports if population-based studies were not available) across a range of settings, with high and low stillbirth rates.

Regions with High Stillbirth Rates

Causes of stillbirth reported in four studies (three of which were hospital based) from countries with high stillbirth rates using different systems are shown in Fig. 6.7 [10, 21, 56, 80]. The stillbirth rate across the countries ranged from 19.5 to 40/1,000 births. The major causes, which varied in proportions across the studies, were: abruption ranging from 24 % to 13 %, hypertension 31–13 %, and intrapartum factors (usually described as hypoxia, obstructed labor) 8–2 %. The categories of maternal conditions ranged from 13 % to 3 % and for congenital abnormality 12–2 %. Less consistently reported were categories of spontaneous preterm birth ranging from 5 % to 2 % and complications of multiple pregnancy (one study only) 2 %. Using ReCoDe, one study in India identified placental causes in 13 % of stillbirth; however, this category was largely made up of abruption. The

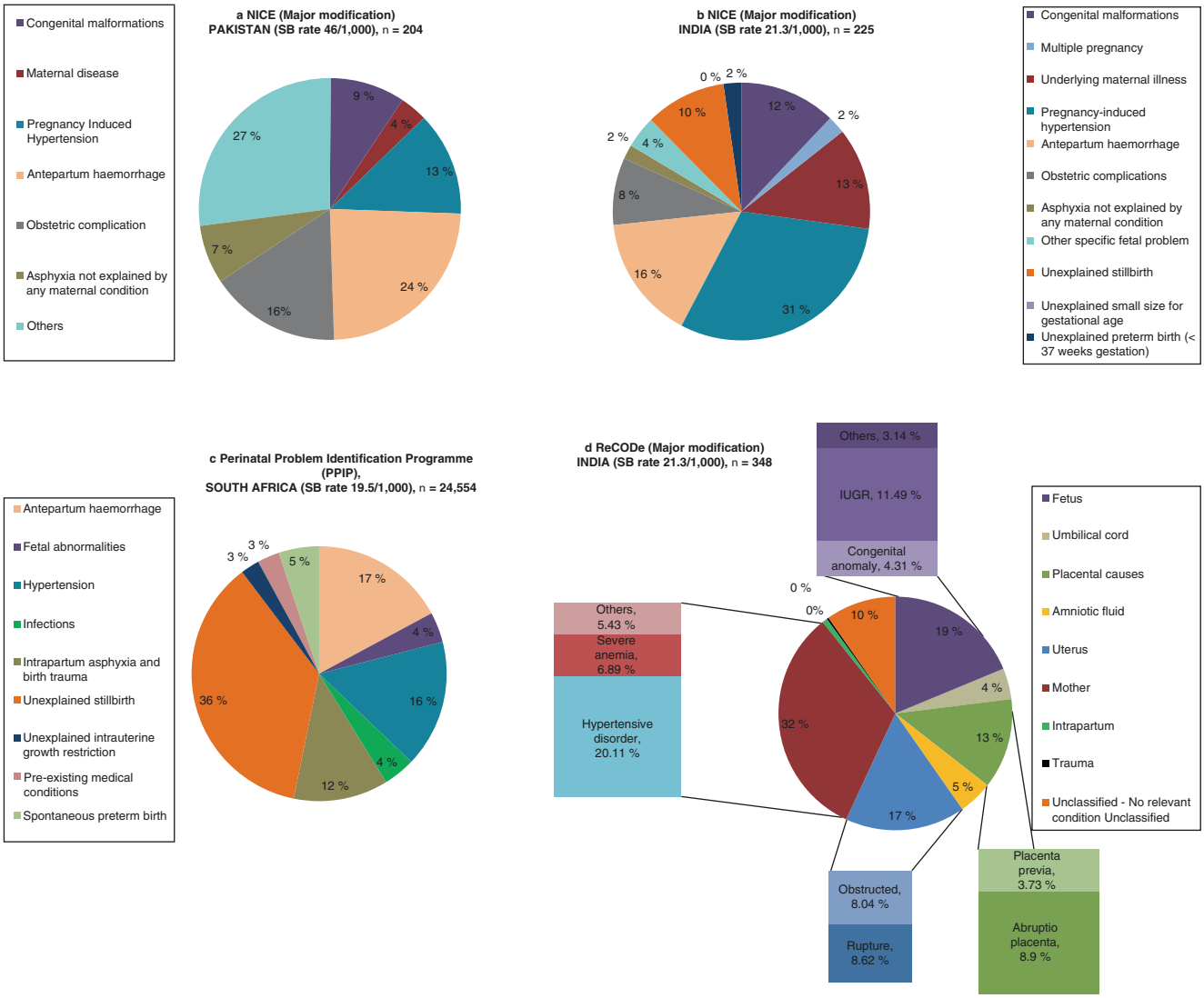


Fig. 6.7 Reported causes of stillbirth from selected studies in regions with high stillbirth rates. Note: **a**, **b**, and **d** are hospital-based studies and **c** is national (Sources: **a**, [56]; **b**, [10]; **c**, [21]; **d**, [80]. *SB rate*: stillbirth rate 28 weeks of gestation or more)

proportion of unexplained stillbirth varied from 36 % to 10 % as did FGR ranging from 10 % to 2 %. One study identified stillbirths attributed to infection with a low proportion (4 %) reported compared with other studies, which may reflect the lack of diagnostic evaluations available in these settings but also variation in population and approach to classification.

In another study, within a research framework, verbal autopsy was used to identify causes in 134 stillbirths across 38 community settings in regions with some of the highest stillbirth rates (up to 46/1,000). A different pattern was shown with 37 % of stillbirths due to infection [60]. This study also reported 10 % of stillbirths as a result of abruption, 14 % due to prolonged/obstructed labor and malpresentation, 7 % as a result of accident, 6 % cord prolapse/complication; 12 % other conditions (including hypertension and multiple pregnancy); and 12 % a low proportion of unexplained (although this may have been due to operator bias in the research setting in which the study was performed). The high proportion of stillbirths due to infection in this study is consistent with other studies in LIC with the main organisms responsible being the Gram-negative organisms (*Klebsiella pneumonia*, *Escherichia coli*) and also syphilis, malaria [81], and human immunodeficiency virus (HIV) in some regions.

All these studies reported a low proportion of stillbirth attributed to intrapartum events. However, a study in Tanzania (with a high perinatal death rate) showed that 43 % of perinatal deaths were due to intrapartum complications [82]. The classification of stillbirth as antepartum, or potentially amenable to interventions at antenatal care, versus intrapartum, or those that require improved obstetric care, is a basic

Cause of death *Level I categories*	%	Contributing as COD or associated condition %	%	*Level II subcategories*
Infection	**14**	16	12	Unspecified
			2	Bacteria – other
Intrapartum	**5**	7	4	Extreme prematurity
Congenital anomalies	**7**	10	3	Unspecified
			2	Cardiovascular and lympathic vessels
			2	Triploidies
			2	Aneuploidies – other
Fetal	**3**	7	4	Unspecified
Cord	**8**	15	2	Knots
			4	Loops
			2	Abnormal insertion
			2	Focal anomaly
			3	Generalized anomaly
			2	Infection / inflammation
Placenta	**26**	56	12	Infection / inflammation
			14	Abruption or retroplacental hematoma
			13	Infarctions and thrombi
			6	Circ. disorders – other non-abruptions
			3	Transfusion or feto-maternal hemorrh.
			4	Small for gestation placenta
			3	Villous / vascular maldevelopment
Maternal	**8**	26	2	Unspecified or other
			11	Hypertensive disorder
			2	Cervix insufficiency
			2	Hematology – other
			6	Diabetes
			2	Autoimmune – other
Unknown	**29**	29	11	- lacking examinations / documentation
			10	- with no autopsy
			5	- despite autopsy and placental PAD
			4	- despite full evaluation
Associated perinatal	**na**	31	11	Small for gestational age
			4	Oligohydramnios
			8	PPROM
			2	Multiples
			2	Antepartum haemorrhage
			5	Sub-optimal care
Associated maternal	**na**	12	3	Smoking
			6	Maternal BMI ≥ 30
			2	Obstetric history
			2	Recreational and addictive drugs

The line connectors illustrate the clinical scenarios of combined factors found in ≥ 2 % of cases, and the thickness of the line illustrates frequency. The slimmest and thickest lines represent 2 % and 7 %, respectively.

Fig. 6.8 Causes and associated conditions in high-income countries, using the Codac system (Reprinted with permission from Flenady et al. [30])

classification that can inform public health interventions. Most studies suggest that about half of stillbirths in LIC occur intrapartum.

Regions with Low Stillbirth Rates

Results from a multicountry study across high-income country settings using the Codac system [30] showed the following major causes of 617 stillbirths (22 weeks of gestation or 500 g): placental pathology identified as a cause in 30 % of stillbirths and implicated in 60 % of cases overall, infection 12 %, cord complications 9 % as causative and a further 8 % as contributory, maternal medical disorders 7 % as caused and as contributing factors in 24 % of cases (most frequent conditions were hypertensive disorders and diabetes), intrapartum events 3 % (overall, 9 % of stillbirths occurred intrapartum, but the causes had antepartum origin for most), and congenital anomalies identified as causal in 6 % and contributory in another 5 %. Fetal maternal hemorrhage, which has been reported to cause 5–14 % of stillbirths, was only detected in 2 % of cases (Fig. 6.8).

Despite thorough investigation, 11 % were unexplained and a further 19 % were classified as unknown due to insufficient investigation. Classification in Codac does not allow FGR as a cause of death; however, it was found to be a contributing factor in 11 % of stillbirths. The low rates of infection and fetal maternal hemorrhage compared to other studies may be due to inadequate investigation in this cohort; autopsy and placental examinations were undertaken in 45 % and 73 % of cases, respectively.

Causes of stillbirth in another four population-based studies from HIC using different systems revealed marked variation in the contribution of conditions (Fig. 6.9) [6, 22,

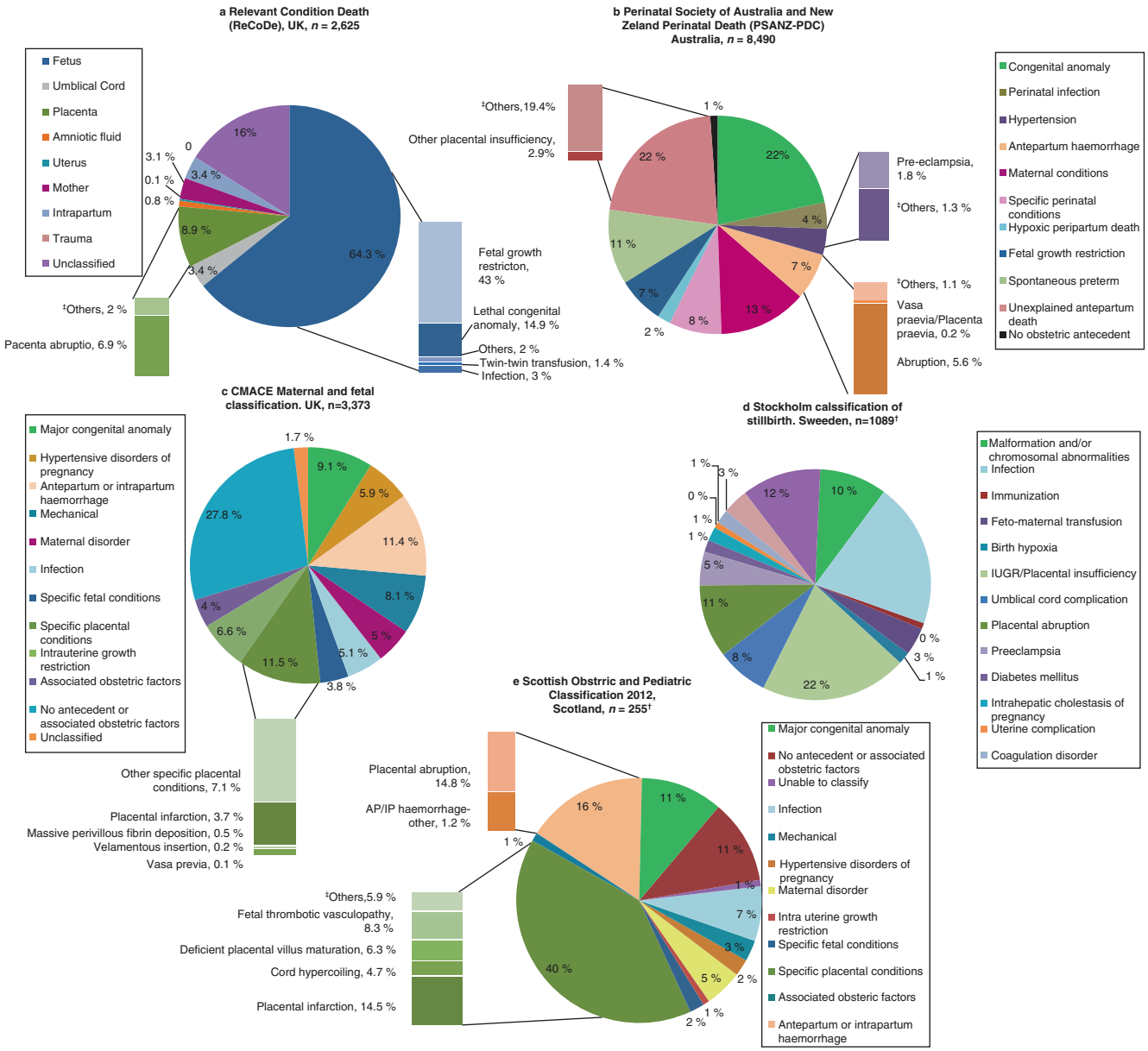


Fig. 6.9 Reported causes of stillbirth from selected studies in regions with low stillbirth rates. The stillbirth rates 28 weeks of gestation or more per 1,000 births in 2012 were as follows: (**a**) and (**d**) the UK 3.4; (**b**) Australia 2.8; (**c**) Scotland 3; (**e**) Sweden 2.7. Rates are taken from Lawn et al. [6]; ‡The remaining subcategories have been added and are included in "others"; € excludes termination of pregnancy; † excludes multiple pregnancy. All the studies are population based (Sources: **a**, [66]; **b**, [28]; **c**, [22]; **d**, [83]; **e**, [49, 72])

28, 49, 66, 72, 83]. Although the stillbirth rates were similar, differences in investigation levels and possible differences in population characteristics may account for this variation. However, a more likely reason for the variation is differences in the classification systems used; one system (ReCoDe) aims to identify relevant conditions as opposed to causes using a hierarchy [66] and conditions varied across the systems. Despite this, a number of common conditions were evident, albeit with varying reported contributions, as follows: placental conditions ranging from 40 % to 9 %; congenital abnormality 22–10 %; infection 22–3 %; and fetal growth restriction from 43 % to 0.8 %. Other reported conditions with less variability across these studies were: cord complications (variously defined) ranging from 9 % to 2 %, maternal hypertensive disorders from 0.8 % to 6 %, and maternal diabetes from 2.8 % to 1 %. Stillbirths as a result of intrapartum events made up a small proportion of stillbirths 3.4–0.7 %. In two studies, twin-twin transfusion syndrome was reported to cause 3 % and 1 % of stillbirths, and in two well-investigated cohorts of stillbirths, feto-maternal transfusion was reported in 5 % [84] and 3 % [83].

The proportion of unexplained, or unknown, ranged from 11 % [72] to 28 % [85] across these studies. The impact of the level of investigation on this variation is difficult to assess. Three studies with high rates of autopsy (95–100 %) and placental histopathology (70–100 %) reported low but varying proportions of unexplained stillbirth: 12 %, 23 %, and 24 %. Applying the Scottish system to a large cohort of singleton stillbirth in Scotland, 11 % were unexplained with a lower autopsy rate (58 %) but comparable rates of placental pathology of 97 %, pointing to the importance of placental examination for stillbirths.

In a multisite research study in the USA using a new system (INCODE) [84], following a full examination of the baby (including autopsy and placental pathology), a probable cause was found in 60 % of stillbirths and more than one probable or possible cause was found in 31 % of cases; 24 % remained unexplained. The main conditions were similar to those reported in the aforementioned cohort studies as follows: obstetric complications 29 % (including abruption 7 %, complications of multiple gestation 6 %), placental abnormalities 24 %, fetal genetic/structural abnormalities in 14 %, infection in 13 %, umbilical cord abnormalities 10 %, hypertensive disorders 9 %, and maternal medical complications 8 % (data not shown). The scenarios of preterm labor, preterm premature rupture of membranes, and cervical insufficiency, often in combination with chorioamnionitis, were implicated in 15 % of stillbirths, which is similar to results when using the Codac system (often leading to intrapartum death) [30] and the PSANZ-PDC system in Australia [86].

Differing approaches to classifying plays an important role in the reported causes of death. For example, the PSANZ-PDC system, which prioritizes classification of congenital abnormality over any other condition, results in almost double the proportion of these conditions compared with other systems. Similarly, the hierarchical ReCoDe system results in a much higher proportion of FGR as it is high in the list of conditions (43 % versus 4 % for the next highest reported frequency). In another hospital-based study in the Netherlands [78], the Tulip system (when applied to a well-investigated cohort of stillbirths) resulted in a low proportion of stillbirths assigned to infection and unexplained, which may have been due to a shift to the category of placental conditions that were reported to cause 64 % of stillbirths.

Differences According to Gestation

Depending on definition used, about half of all stillbirths occur at less than 28 weeks in HIC. Causes of stillbirth differ by gestational age. Infection-related stillbirth has been shown to be more frequent in pregnancies at early gestations. In the aforementioned Codac study [30], infections contributed to 6 % of stillbirths at 28 weeks of gestation or more and to 15 % of stillbirths at less than 28 weeks in most cases in scenarios of chorioamnionitis and preterm prelabor rupture of membranes (PPROM), often leading to intrapartum deaths. However, other studies have shown that infection plays an important role in term and post-term pregnancies [83].

Causes of Neonatal Deaths Globally

The major causes of neonatal deaths globally were reported recently in *The Lancet*'s newborn series [6] (Fig. 6.10). In 2012, complications from preterm birth (36 %), intrapartum-related conditions (23 %), and infections (23 %) were the main causes of neonatal deaths globally. The main infections were sepsis, meningitis, and pneumonia. In the early neonatal period, two major categories made up the majority (70 %) of deaths: intrapartum-related conditions (almost one-third) and preterm birth (40 %). Infections were responsible for half of the late neonatal deaths. The cause-specific risk varies substantially across regions by the neonatal mortality rates. Regions with a higher neonatal mortality rate have a higher proportion of deaths from infection, which are largely preventable, compared with regions of lower mortality where causes relate to preterm birth and congenital abnormalities. Preterm birth is a major contributor to neonatal death worldwide with increasing rates in most countries [88].

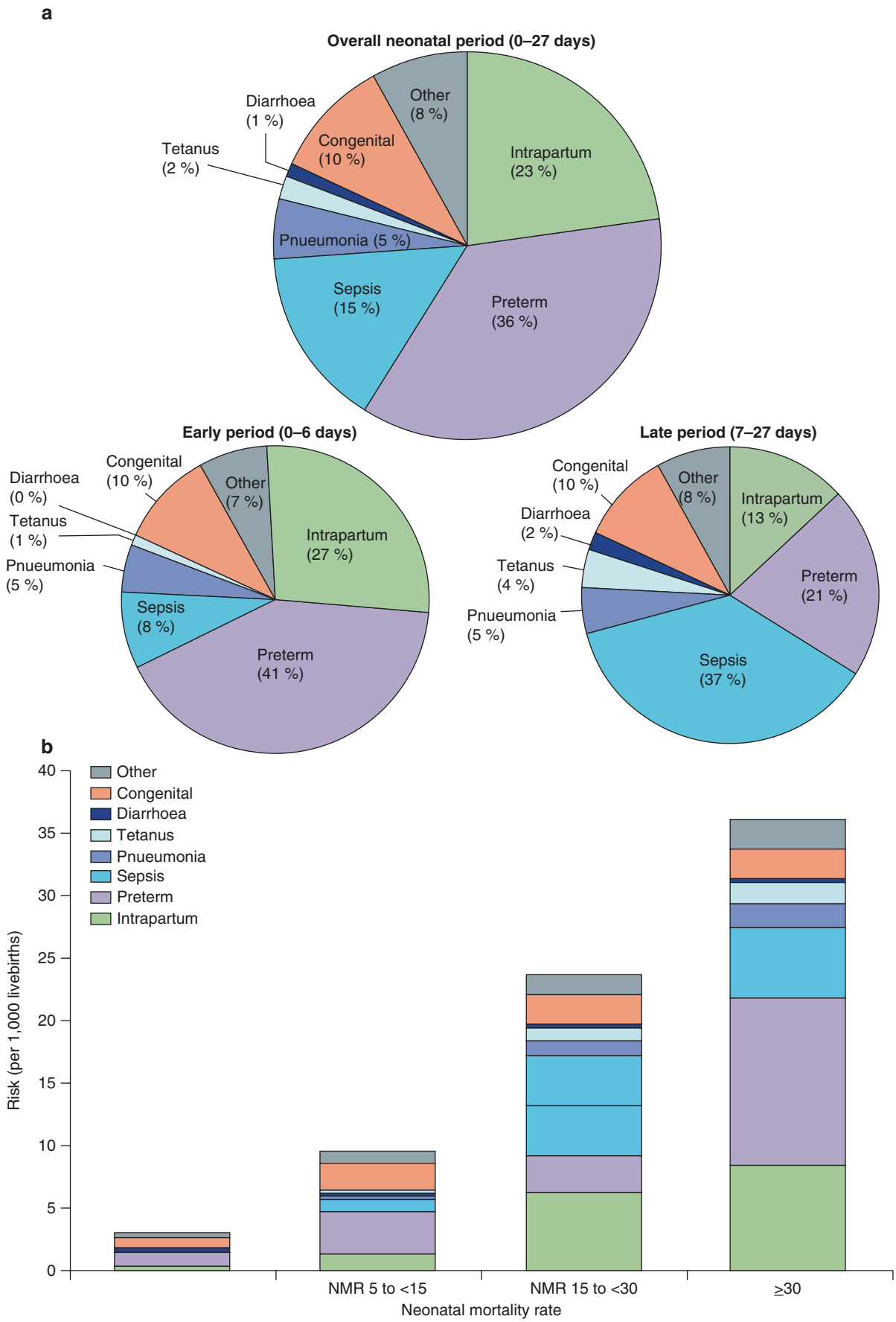
Neonatal Deaths in Low Mortality Settings

A regional report from Australia provides a detailed breakdown of causes of neonatal deaths, with the majority of neonatal deaths relating to extreme prematurity (deaths in nonviable or marginally viable infants) and complications of prematurity in those admitted for intensive care and congenital abnormality [86] (Fig. 6.11).

Disparity

Differences in patterns of perinatal death are evident by ethic/racial background. A recent study in Australia [31] reported the gap in stillbirth rates between indigenous and non-indigenous women is closing, but indigenous women continue to be at increased risk due to a number of poten-

Fig. 6.10 Causes of neonatal death globally. Cause of death distribution for the neonatal period, and by the early (<7 days) and late (7–28 days) neonatal periods, for 194 countries in 2012 and (**b**) variation in cause-specific neonatal mortality rates (NMRs) by level of NMR in 2012, showing risk difference by cause of death compared with the lowest mortality group (NMR<5) (Reprinted with permission from Lawn et al. [6]). Based on data from: Oza et al. [87])


a
Overall neonatal period (0–27 days)
Other (8 %)
Diarrhoea (1 %)
Congenital (10 %)
Tetanus (2 %)
Intrapartum (23 %)
Pnueumonia (5 %)
Sepsis (15 %)
Preterm (36 %)
Early period (0–6 days)
Congenital (10 %)
Other (7 %)
Diarrhoea (0 %)
Tetanus (1 %)
Intrapartum (27 %)
Pnueumonia (5 %)
Sepsis (8 %)
Preterm (41 %)
Late period (7–27 days)
Congenital (10 %)
Other (8 %)
Intrapartum (13 %)
Diarrhoea (2 %)
Tetanus (4 %)
Preterm (21 %)
Pnueumonia (5 %)
Sepsis (37 %)
b
Other
Congenital
Diarrhoea
Tetanus
Pnueumonia
Sepsis
Preterm
Intrapartum
Risk (per 1,000 livebirths)
0
5
10
15
20
25
30
35
40
NMR 5 to <15
NMR 15 to <30
≥30
Neonatal mortality rate

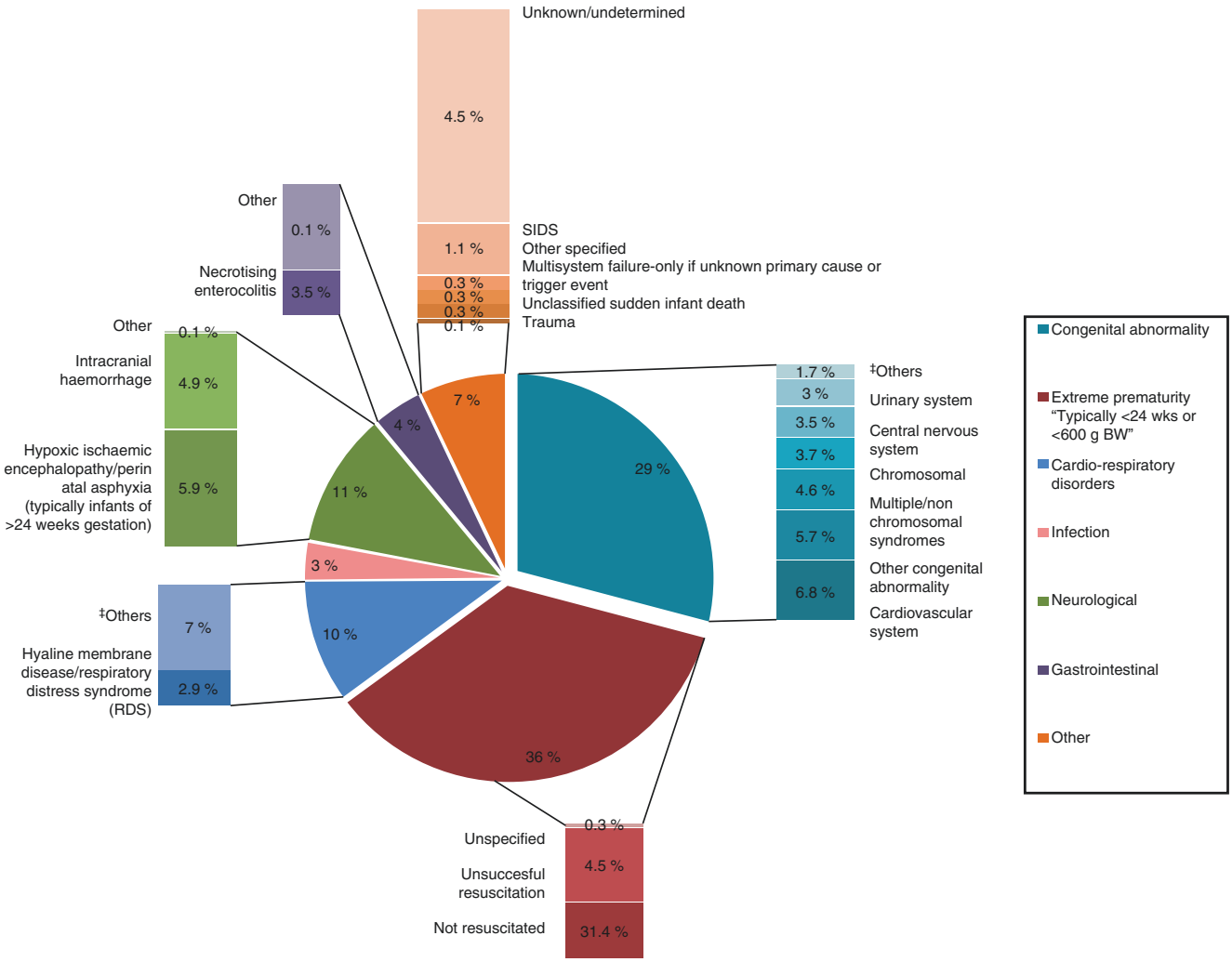


Fig. 6.11 Causes of neonatal death using PSANZ neonatal death classification, Queensland, Australia 2009–2011, $n = 694$ (Adapted from [86]. ‡The remaining subcategories have been added and are included in "others". *BW* birthweight)

tially preventable conditions. Major conditions contributing to the disparity were maternal conditions (diabetes), perinatal infection, spontaneous preterm birth, hypertension, fetal growth restriction, and antepartum hemorrhage. Among indigenous women, regional and remote locations are increased risk factors compared with urban location. While reductions were shown in the rates of stillbirth at preterm gestations, no reduction was seen for term stillbirths [31]. In a recent US study, a higher proportion of stillbirths in non-Hispanic black women compared with non-Hispanic white and Hispanic women are associated with obstetric complications and infections. Stillbirths occurring intrapartum and early in gestation were more common in non-Hispanic black women [84]. Women living in rural regions of the world have higher rates of adverse pregnancy outcome [7].

Contributing Factors

The major contributors to adverse pregnancy outcome globally are presented in Table 6.3 [51]. The contributing factors (risk factors) for stillbirths in HIC were recently comprehensively reported in *The Lancet* [89] and are summarized here, with additional reports from LMIC-country research.

Maternal Demographic Factors

Lower socioeconomic status (SES) is universally associated with an increased risk of stillbirth and neonatal death. SES is interrelated with other socioeconomic factors such as education, employment, income, and marital status. Lower

Table 6.3 Major risk factors for adverse pregnancy outcome

	Adjusted odds ratio[a]
Life-cycle factors	
Maternal age (years)	
<18	1.1–2.3
>35	1.3–2.0
Maternal size	
Height <150 cm	1.3–4.8
Pre-pregnancy weight <47 kg	1.1–2.4
Parity	
Primigravida	1.3–2.2
Parity >6	1.4–1.5
Poor obstetric history (previous perinatal death or instrumental delivery)	1.6–3.5
Antenatal factors	
Multiple pregnancy	2.0–6.8
Hypertensive disorders	
Preeclampsia	1.7–3.7
Eclampsia	2.9–13.7
Bleeding per vagina after 8th month	3.4–5.7
Maternal jaundice	2.0–7.9
Maternal anemia (PCV <0.21)	1.9–4.2
Maternal anemia (PCV <33 %)	NS in 4 studies
Maternal malaria (blood test positive)	2.2–3.5[b]
Syphilis (perinatal death)	1.7–5.8
HIV (infant death)	7.2
Intrapartum factors	
Malpresentation	
Breech	6.4–14.7
Others	8.3–33.5
Obstructed labor/dystocia	6.7–84.9
Prolonged second stage	2.6–4.8
Maternal fever during labor (>38 °C)	9.7–10.2
Rupture of membranes >24 h	1.8–6.7
Meconium-stained liquor	11.5

Reprinted with permission from Table 3, Lawn et al. [51]
PCV packed cell volume, *NS* not significant
[a]Odds ratios included are from population-based studies adjusting for major confounders (parity and socioeconomic status) and significantly associated with intrapartum stillbirth or neonatal death or perinatal death unless given as NS in more than one study
[b]Risk for low birthweight not mortality

educational attainment itself is an important socioeconomic marker associated with stillbirth and neonatal death across a diverse range of settings [90]. In high-income country settings, low education (usually defined as ≤10 or ≤8 years) carries an approximate 70 % increase in the odds of stillbirth. Population attributable risk (PAR) for low education and stillbirth has been estimated at 5 % in HIC overall as high as 50 % in LMIC [91].

The association of race and ethnic background in adverse pregnancy outcome is well established in HIC. In the USA, black race is independently associated with stillbirth and neonatal deaths. In Australia, population estimates show that indigenous women have around twice the rate of stillbirth and neonatal death of non-indigenous women. However, when controlling for maternal and medical factors, Australian indigenous status was shown not to be independently associated with stillbirth, highlighting the avoidability of these deaths. Disparity in stillbirths and neonatal deaths between the richest and poorest population across HIC persists [24, 92]. Similarly, data from sub-Saharan Africa and countries in south Asia reveal consistently higher neonatal death rates for the poorest families [93]. Other ethnic minorities are also at increased risk in both HIC [94] and LMIC [90].

Inadequate antenatal care (defined as either late or low attendance) is associated with stillbirth in both HIC [89, 95] and LMIC [90], with a three- to sevenfold increase in the odds compared to those with adequate antenatal care. Important disparity continues to exist with women from disadvantaged backgrounds having poorer antenatal care attendance [90]. Globally, families living in rural areas, where there is limited access to appropriate healthcare, have an increased risk of adverse outcome [7]. The highest neonatal death rates occur in regions with low coverage of skilled birth attendance and institutional delivery [93]. A study in Canada [96] found a 40 % increased risk of stillbirth in isolated rural areas.

While advanced maternal age is associated with higher rates of obesity, acquired medical conditions such as diabetes, infertility, the use of reproductive technologies, and multiple gestations [97], it also is an important independent risk factor for stillbirth. In HIC, a 70 % increase in the odds of stillbirth has been shown for women of 35 years or older and a doubling of the odds for women over 40. In LMIC settings, a doubling of the odds of stillbirth for women over 35 and a fivefold increase for women over 40 have been reported [90]. The risk of stillbirth increases with gestational age [98], and for women of advanced age, the risk is more evident in late gestation [99, 100]. In HIC settings, young maternal age (<20 years) does not appear to be an independent risk factor for stillbirth; however, extremely younger age groups in the USA have been shown to carry an increased risk. In LMIC, young maternal age also is a contributor to stillbirth and neonatal death [90].

Primiparity is associated with a similar increase in the odds of stillbirth across high-, low-, and middle-income settings ranging from around a 30 % to 60 % increase [89, 90]. PAR for stillbirths attributed to primiparity in HIC has been estimated at around 15 %, highlighting its importance as a contributor to stillbirth. In LMIC and HIC, multiparty of five or more births carries increased odds of stillbirth [89, 90] and other adverse pregnancy [93]. With very low prevalence in

HIC, grand multiparity makes a very small contribution to stillbirth rates. However, in some populations, multiparity may play a bigger role due to higher prevalence. In HIC, the number of women delaying childbearing is rising, increasing the proportion of primiparous women of advanced age. Although few studies have rigorously addressed the interaction of these two factors, stillbirth risk in older primiparous women (i.e., ≥35 years) may be two to fourfold higher than their counterparts [89].

The association between interpregnancy interval and adverse outcome in a HIC setting is unclear. Although a 30 % increase in the odds of stillbirth was associated with an interval of 3 years or more compared with 1 to less than 3 years in one study [101], another study showed a 50 % increase for an interval of 6 years or more compared with 3–5 years [102]. In some LMIC an unmet need for family planning is a contributor to adverse outcome.

Maternal Weight and Nutrition

Obesity is a major potentially avoidable risk factor to stillbirth in HIC and emerging risk factor in poorer settings, with increased access to caloric dense but nutrient poor food. Maternal pre-pregnancy overweight and obesity (combined body mass index [BMI] 25–30 and >30, respectively) are associated with stillbirth. In HIC, BMI of 25–30 has been associated with a 30 % increase in the odds for stillbirth, BMI >30 a 60 % increase, and BMI >40 a more than twofold increase in the odds for stillbirth. PAR for maternal overweight and obesity in HIC is estimated at 12 %. With higher prevalence, PAR for indigenous Australian and Canadian women and for African American women is estimated at 20 %, 25 %, and 23 %, respectively. In one study, women who gain three or more units in BMI (independent of whether they were overweight in the first pregnancy) between the first and second pregnancies had a 60 % increase in the odds of stillbirth. The effect was stronger for term than for preterm births, suggesting a relationship between BMI and placental function. In LMIC, maternal underweight and poor nutrition leading to anemia increase the risk of stillbirth and neonatal death [93].

Smoking

Smoking has tremendous global impact on health and, in pregnancy, appears causally associated with stillbirth [101]. In high-income countries, smoking during pregnancy has been associated with a 40 % increase in the odds of stillbirth, and with almost double the risk for heavy smoking (greater than or equal to ten cigarettes per day). PAR for any smoking was conservatively estimated at 8 %. Assuming the same strength of association, with a much higher prevalence of 50–60 % [103], PAR for indigenous Australian and Canadian women is estimated to be around 20 %[89]. Smoking cessation programs in pregnancy are the only intervention shown to reduce preterm birth and low birthweight, but uptake into practice is variable [104].

Alcohol, Illicit Drug Use

While the adverse effects of alcohol consumption on the developing fetus are well accepted, there is a paucity of high-quality data to assess its impact [105]. Meta-analysis of two studies in HIC [106, 107] showed a small (10 %) increase in the odds of stillbirth for low intake (one to three drinks per week). One large study in the USA [106] showed the association was stronger for stillbirth <28 weeks of gestation (80 % increase in the odds). However, the risk was isolated to women with greater than five drinks per week. Based on a prevalence of 50 % and 40 % increased risk, PAR for alcohol could reach 17 %. Three or more episodes of binge drinking in the first trimester have been associated with a 45 % increase in the odds of stillbirth [107]. A doubling of the odds of stillbirth has been reported for women using illicit drugs in pregnancy. While good-quality prevalence data, is lacking using a prevalence of 2.4 % [108], the PAR for stillbirth is estimated at 2 % in HIC. The contribution is higher in poorer communities.

Birthweight and Preterm Birth

Both high birthweight and low birthweight are associated with adverse pregnancy outcome [109]. Globally, low birthweight (<2,500 g) either due to preterm birth or small for gestational age (SGA) or both is the major contributor for more than 80 % of neonatal deaths and is also strongly linked with later mortality and morbidity including adult-onset noncommunicable diseases [6]. Prematurity alone is a major indirect cause for neonatal death carrying a huge burden of disease globally [88]. Of preterm births, those born less than 32 weeks of gestation are at highest risk in the short and longer term. Suboptimal fetal growth is also strongly associated with stillbirth. In HIC SGA <10 % is associated with a fourfold increased risk of stillbirth with a PAR of 23 %.

Previous Obstetric History

Previous stillbirth is associated with around a threefold increase in the odds of subsequent stillbirth in HIC and is also an important risk factor in LMIC [90]. Women who have a previous preterm SGA birth are at increased risk of stillbirth in a subsequent pregnancy with the risk increasing with

decreasing gestational age of the previous birth ranging from aOR of 3.4 for 32–36 weeks of gestation to aOR of 5 for less than 32 weeks. Previous cesarean section has been shown to be associated with a 30–50 % increase in the odds of stillbirth. While confounding due to the recurrence risk of medical conditions and pregnancy complications cannot be excluded, this finding is concerning given the increasing rates of cesarean births. Cesarean section may involve the major blood vessels, including the uterine arteries and its major branches, and this could affect perfusion of the uterus in future pregnancies. Moreover, many stillbirths are thought to be causally related to abnormal placentation, and previous cesarean section is a known risk factor for other placentally related complications, such as abruption.

Maternal Medical Conditions and Pregnancy Complications

Maternal medical conditions and pregnancy complications may be causal or contributory in perinatal deaths. Data from HIC shows that while overall contribution of preexisting diabetes to stillbirths is small at the population level (PAR 3–5 %), it is one of the maternal medical conditions most strongly associated with stillbirth. Despite modern obstetrics, diabetes is associated with a threefold increase in the odds of stillbirth. Chronic/preexisting hypertension remains an important contributor to adverse pregnancy outcome with almost three times the odds of stillbirth in HIC [89]. Preeclampsia is associated with a 60 % increase in the odds of stillbirth with a PAR of around 3 %. A threefold increase in the odds has been reported for severe preeclampsia [110]. Pregnancy-induced hypertension (gestational hypertension) is associated with a 30 % increase in the odds of stillbirth [89]. A strong association with placental abruption and stillbirth is clear; the PAR for abruption is estimated at 15 %. These conditions are also associated with preterm birth and neonatal deaths and play a much bigger role in LMIC where access to quality antenatal care is lacking. Multiple pregnancy is a strong risk factor independently associated with stillbirth and neonatal death. Bateman et al. [111] in the USA reported a sixfold increase in the odds of stillbirth, and an Australian study [95] reported a threefold increase in odds for twin or multiple pregnancies. Post-term pregnancy (≥42 weeks) is an independent risk factor for adverse pregnancy outcome.

Other Factors

The currently available data suggest that women conceiving using assisted reproductive technology are likely to be at increased risk of neonatal deaths through SGA and preterm birth. The association of assisted reproductive technology with stillbirth is unclear [112]. In LMIC, environmental and indoor pollution has been shown to be associated with stillbirth [90]. No clear association with stillbirth and gender is apparent [90]. While girls have a lower risk of neonatal death than boys, they have a higher social risk in some countries [6]. Consanguinity is a risk factor for stillbirth in some regions and cultures [90].

Substandard Care

Studies have consistently shown that suboptimal antenatal and obstetric care are frequently associated with stillbirths and neonatal deaths, ranging from 10 to 60 % of cases [30]. The main reported factors relate to delayed recognition of emerging clinical disorders and, if noted, an inadequate or delayed response. Other factors include failure to use updated best practice protocols, poor communication between staff, inadequate antenatal care attendance, inadequate diabetes management, and maternal smoking. Although intrapartum stillbirths now make up a small proportion of late gestation stillbirths in high-income countries, concerns have been raised regarding the contribution of suboptimal care in these cases. In South Africa, the PPIP [21] reported that almost half of the deaths due to intrapartum asphyxia were probably preventable with better fetal monitoring and use of the partogram and the second stage of labor. Other factors included inadequate facilities in spontaneous preterm labor and care of the newborn, hypertension that was detected but not acted upon, and lack of response to poor fetal movements. One of the most commonly reported avoidable factors relating to stillbirths is the failure to detect or act upon poor fetal growth during antenatal care [113]. In LMIC, high fertility rates coupled with low coverage of care and access to family planning are major contributors to stillbirth and neonatal death [93]. Other avoidable deaths include those from infections and intrapartum-associated disorder, which still account for a high proportion of deaths, especially among the poorest families, despite the availability of low-tech interventions.

Conclusion

In this chapter we have reported rates of perinatal death globally, the vast majority occurring in low- and middle-income countries where upscaling of known effective interventions could avoid the majority of these deaths. Conditions at birth and those arising in the early newborn period account for almost 10 % of the global burden of disease. The United Nations' Millennium Development Goal 4 (MDG 4) is to reduce the 1990 childhood mortality levels by two-thirds by the year 2015. As neonatal deaths make up 44 % of all child deaths globally [6], reducing neonatal deaths is paramount to achieving this

target. The absence of stillbirth in the MDG has resulted in a lack of focus on prevention of these deaths and slow progress [6]. The reduction in neonatal death rates has been slower than for child deaths and even slower for stillbirths in both poor and well-resourced settings.

Placental pathology and fetal growth restriction are important contributors to stillbirth and neonatal death. Obesity is a major potentially avoidable risk factor to stillbirth in high-income countries and emerging risk factor in poorer settings. Preterm birth is an important contributor to neonatal deaths across all settings. The epidemiological method can assess ways in which perinatal mortality rates are higher than expected and can inform appropriate preventive strategies. However, poor-quality data plague such analyses. Lack of registration of births and deaths in low- and middle-income countries is a major problem, and the numerous definitions used render monitoring across and within countries problematic. Further, suboptimal data systems pose a significant barrier to monitoring interventions aimed at preventing perinatal deaths. High-quality investigation and audit are needed to identify causes and contributing factors in perinatal deaths but this is often lacking. The reported causes of stillbirth and neonatal death vary widely. With no single classification system clearly superior, a new global system is needed. The WHO is currently developing such a system to address this current deficiency. This system will align with the ICD 11 revision and follow procedures used for the development and implementation of the WHO ICD Maternal Mortality [76].

References

1. Anonymous. Random House Kernerman Webster's College Dictionary. 2010.
2. Walker KF, Cohen AL, Walker SH, Allen KM, Baines DL, Thornton JG. The dangers of the day of birth. BJOG. 2014;121:714–8.
3. Frøen JF, Cacciatore J, McClure EM, Kuti O, Jokhio AH, Islam M, et al. Stillbirths: why they matter. Lancet. 2011;377:1353–66.
4. Cacciatore J. Psychological effects of stillbirth. Semin Fetal Neonatal Med. 2013;18:76–82.
5. Anonymous. World Health Organization. 2011. Available from: http://www.who.int/healthinfo/statistics/indneonatalmortality/en/.
6. Lawn JE, Blencowe H, Shefali O, Danzhen Y, ACC L, Peter W, et al. Every newborn: progress, priorities, and potential beyond survival. Lancet. 2014;384:189–205.
7. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Stillbirths: where? When? Why? How to make the data count? Lancet. 2011;377:1448–63.
8. Leisher S, Reinebrant H, Flenady V. Who global classification systems for stillbirth and neonatal death workshop of the international conference on stillbirth, sids and baby survival. Amsterdam; 2014.
9. Frøen JF, Pinar H, Flenady V, Bahrin S, Charles A, Chauke L, et al. Causes of death and associated conditions (Codac) – a utilitarian approach to the classification of perinatal deaths. BMC Pregnancy Childbirth. 2009;9:22–34.
10. Aggarwal AK, Jain V, Kumar R. Validity of verbal autopsy for ascertaining the causes of stillbirth. Bull WHO. 2011;89:31–40.
11. Katz DL, Elmore JG, Wild DMG, Lucan SC. Birth outcomes: a global perspective. Epidemiology, biostatistics, preventive medicine, and public health. Philadelphia: Elsevier; 2013.
12. Flenady V, King J, Charles A, Gardener G, Ellwood D, Day K, et al. Clinical practice guideline for perinatal mortality. Brisbane: Perinatal Society of Australia and New Zealand; 2009.
13. Kirby RS. The coding of underlying cause of death from fetal death certificates: issues and policy considerations. Am J Public Health. 1993;83:1088–91.
14. Australian Bureau of Statistics. Deaths Australia, November 2008. Canberra: Australian Bureau of Statistics; 2010.
15. Measey MA, Charles A, d'Espaignet ET, Harrison C, Deklerk N, Douglass C. Aetiology of stillbirth: unexplored is not unexplained. Aust N Z J Public Health. 2007;31:444–9.
16. Porta M. A dictionary of epidemiology. 6th ed. Oxford: Oxford University Press; 2014.
17. GRADE Working Group. Grading quality of evidence and strength of recommendations. Br Med J. 2004;328:1490–3.
18. Golding J. Epidemiology of fetal and neonatal death. In: Keeling JW, editor. Fetal and neonatal pathology. London: Springer; 2001. p. 175–90.
19. Martines J, Paul VK, Bhutta ZA, Koblinsky M, Soucat A, Walker N, et al. Neonatal survival 4 – neonatal survival: a call for action. Lancet. 2005;365:1189–97.
20. Anonymous. Indepth network. [Cited 25 Nov 2014]; Available from: http://www.indepth-network.org.
21. Pattinson RC, Rhoda N. Saving babies 2012–2013: ninth report on perinatal care in South Africa. Pretoria: Tshepesa Press; 2014. Available from: www.ppip.co.za.
22. Centre for Maternal and Child Enquiries. Perinatal mortality 2008. London; 2010.
23. Eskes M, Waelput AJM, Erwich JJHM, Brouwers HAA, Ravelli ACJ, Achterberg PW, et al. Term perinatal mortality audit in the Netherlands 2010–2012: a population-based cohort study. BMJ Open. 2014;4:e005652–62.
24. Health Safety and Quality Commission, published in Wellington in 2014: Perinatal and maternal mortality review committee. Eighth annual report of the perinatal and maternal mortality review committee, reporting mortality 2012. Health Safety and Quality Commission, Wellington, NZ, 2014.
25. Buchmann EJ. Towards greater effectiveness of perinatal death audit in low and middle-income countries. BJOG. 2014;121:134–6.
26. Butler NR, Bonham DG. Perinatal mortality. Edinburgh and London. In: Report of the 1958 British perinatal mortality survey. Edinburgh: E and S Livingstone; 1963. p. 202–5.
27. Ashley D, McCaw-Binns A, Golding J, Keeling J, Escoffery C, Coard K, et al. Perinatal survey in Jamaica: aims and methodology. Paediatr Perinat Epidemiol. 1994;8:6–16.
28. Hilder L, Li Z, Zeki R, Sullivan EA. Stillbirths in Australia 1991–2009. Sydney; 2014.
29. Gregory ECW, MacDorman MF, Martin JA. Trends in fetal and perinatal mortality in the United States, 2006–2012 NCHS Data Brief. 2014. p. 169.
30. Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. Lancet. 2011;377:1703–17.
31. Ibiebele I, Coory M, Boyle FM, Humphrey M, Vlack S, Flenady V. Stillbirth rates among indigenous and non-indigenous women in Queensland, Australia: is the gap closing? BJOG. 2014, doi:10.1111/1471-0528.13047.
32. Joseph KH, Kinniburgh B, Jennifer A, Hutcheon, Azar M, Basso M, Davies C, Lee L. Determinants of increases in stillbirth rates from 2000 to 2010. CMAJ. 2013;185:E-345–51.

33. Wigglesworth JS. Monitoring perinatal mortality. A pathophysiological approach. Lancet. 1980;2:684–6.
34. Flenady V, Frøen JF, Pinar H, Torabi H, Saastad R, Guyon G, et al. An evaluation of classification systems for stillbirth. BMC Pregnancy Childbirth. 2009;9:24–36.
35. Chan A, King JF, Flenady V, Haslam RH, Tudehope DI. Classification of perinatal deaths: development of the Australian and New Zealand classifications. J Paediatr Child Health. 2004;40:340–7.
36. Gordijn SJ, Korteweg FJ, Erwich JJHM, Holm JP, Van Diem MT, Bergman KA, et al. A multilayered approach for the analysis of perinatal mortality using different classification systems. Eur J Obstet Gynecol Reprod Biol. 2009;144:99–104.
37. Baird D, Walker J, Thomson AM. The causes and prevention of stillbirths and first week deaths. III. A classification of deaths by clinical cause; the effect of age, parity and length of gestation on death rates by cause. J Obstet Gynaecol Br Emp. 1954;61:433–48.
38. Alberman E, Blatchley N, Botting B, Schuman J, Dunn A. Medical causes on stillbirth certificates in England and Wales: distribution and results of hierarchical classifications tested by the office for national statistics. Br J Obstet Gynaecol. 1997;104:1043–9.
39. Amar HSS, Maimunah AH, Wong SL. Use of Wigglesworth pathophysiological classification for perinatal mortality in Malaysia. Arch Dis Child. 1996;76:F56–9.
40. Ashley D, McCaw-Binns A, Foster-Williams K. The perinatal morbidity and mortality study of Jamaica. Paediatr Perinat Epidemiol. 1988;2:138–47.
41. Barson A, Tasker M, Lieberman BA, Hillier VF. Impact of improved perinatal care on the causes of death. Arch Dis Child. 1984;59:199–207.
42. Joshi AR, Daga SR, Daga AS. Perinatal audit through Wigglesworth's classification. Indian Pediatr. 1988;25:525–9.
43. Keeling JW, MacGillivray I, Golding J, Wigglesworth J, Berry J, Dunn PM. Classification of perinatal death. Arch Dis Child. 1989;64:1345–51.
44. Raghuveer G. Perinatal deaths: relevance of Wigglesworth's classification. Paediatr Perinatal Epidemiol. 1992;6:45–50.
45. Settatree RS, Watkinson M. Classifying perinatal death: experience from a regional survey. Br J Obstet Gynaecol. 1993;100:110–21.
46. Tzoumaka-Bakoula C, Lekea-Karanika V, Matsaniotis NS, McCarthy BJ, Golding J. Birthweight specific perinatal mortality in Greece. Acta Paediatr Scand. 1990;79:47–51.
47. Cole S, Hey E, Thomson A. Classifying perinatal death: an obstetric approach. Br J Obstet Gynaecol. 1986;93:1204–12.
48. Whitfield CR, Smith NC, Cockburn F, Gibson AA. Perinatally related wastage – a proposed classification of primary obstetric factors. Br J Obstet Gynaecol. 1986;93:694–703.
49. Scotland NS. Scottish perinatal and infant mortality and morbidity report. Edinburgh: Healthcare Improvement Scotland Reproductive Health Programme; 2012.
50. Hey EN, Lloyd DJ, Wigglesworth JS. Classifying perinatal death: fetal and neonatal factors. Br J Obstet Gynaecol. 1986;93:1213–23.
51. Lawn JE. 4 million neonatal deaths: an analysis of available cause-of-death data and systematic country estimates with a focus on "birth asphyxia". London: University College London; 2009.
52. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010;375:1969–87.
53. Winbo IGB, Serenius FH, Dahlquist GG, Kallen BAJ. NICE, a new cause of death classification for stillbirths and neonatal deaths. Int J Epidemiol. 1998;27:499–504.
54. Anker M, Black RE, Coldham C, Kaltes HD, Quigley MA, et al. A standard verbal autopsy method for investigating causes of death in infants and children. Geneva: WHO; 1999.
55. Aggarwal AK, Jain V, Kumar R. Accuracy of who verbal autopsy tool in determining major causes of neonatal deaths in India. PLoS One. 2013;8:e54865.
56. Nausheen S, Soofi SB, Sadiq K, Habib A, Turab A, Memon Z, et al. Validation of verbal autopsy tool for ascertaining the causes of stillbirth. PLoS One. 2013;8:e76933.
57. Manandhar SR, Ojha A, Manandhar DS, Shrestha B, Shrestha D, Saville N, et al. Causes of stillbirths and neonatal deaths in Dhanusha district, Nepal: a verbal autopsy study. Kathmandu Univ Med J (KUMJ). 2010;8:62–72.
58. The MRC Unit for Maternal and Infant Health Care Strategies and the PPIP Users. Saving babies 2002 third perinatal care survey of South Africa: National Department of Health 2002. Report No.: ISBN 0-620-31041-3.
59. Jehan I. Neonatal mortality, risk factors and causes: a prospective population-based cohort study in urban Pakistan. Bull WHO. 2009;87:130–8.
60. Engmann C, Garces A, Jehan I, Ditekemena J, Phiri M, Mazariegos M, et al. Causes of community stillbirths and early neonatal deaths in low-income countries using verbal autopsy: an international, multicenter study. J Perinatol. 2011;32:585–92.
61. NHS Scotland. Scottish perinatal and infant mortality and morbidity report 2007. Edinburgh: NHS Quality Improvement Scotland; 2008.
62. Varli IH, Petersson K, Bottinga R, Bremme K, Hofsjö A, Holm M, et al. The Stockholm classification of stillbirth. Acta Obstet Gynecol Scand. 2008;87:1202–12.
63. Dudley DJ, Goldenberg R, Conway D, Silver RM, Saade GR, Varner MW, et al. A new system for determining the causes of stillbirth. Obstet Gynecol. 2010;116:254–60.
64. Korteweg FJ, Gordijn SJ, Timmer A, Erwich J, Bergman KA, Bouman K, et al. The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement. BJOG 2006;113:393–401.
65. Anonymous. MBRRACE-UK mothers and babies: reducing risk through audits and confidential enquiries across the UK. London [cited 21 Oct 2014]; Available from: www.npeu.ox.ac.uk/mbrrace-uk.
66. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. BMJ. 2005;331:1113–7.
67. VanderWielen B, Zaleski C, Cold C, McPherson E. Wisconsin stillbirth services program: a multifocal approach to stillbirth analysis. Am J Med Genet Part A. 2011;155:1073–80.
68. Baqui AH, Black RE, Arifeen SE, Hill K, Mitra AN, Sabir AA. Causes of childhood deaths in Bangladesh: results of a nationwide verbal autopsy study. Bull WHO. 1998;76:161–71.
69. Baird D, Thomson AM. The survey perinatal deaths re-classified by special clinico-pathological assessment. Edinburgh: Churchill; 1969.
70. Cole S, Hartford RB, Bergsjo P, McCarthy B. International collaborative effort (ICE) on birth weight, plurality, perinatal, and infant mortality. III: a method of grouping underlying causes of infant death to aid international comparisons. Acta Obstet Gynecol Scand. 1989;68:113–7.
71. Weindling AM. The confidential enquiry into maternal and child health (CEMACH). Arch Dis Child. 2003;88:1034–7.
72. NHS Scotland. Scottish perinatal and infant mortality and morbidity report. Edinburgh: Healthcare Improvement Scotland Reproductive Health Programme; 2014.
73. Kramer MS, Liu S, Luo Z, Yuan H, Platt RW, Joseph KS. Analysis of perinatal mortality and its components: time for a change? Am J Epidemiol. 2002;156:493–7.
74. Reddy UM, Goldenberg R, Silver R, Smith GCS, Pauli RM, Wapner RJ, et al. Stillbirth classification – developing an international consensus for research: executive summary of a National Institute of Child Health and Human Development workshop. Obstet Gynecol. 2009;114:901–14.
75. Ego A, Zeitlin J, Batailler P, Cornec S, Fondeur A, Baran-Marszak M, et al. Stillbirth classification in population-based data and role

of fetal growth restriction: the example of recode. BMC Pregnancy Childbirth. 2013;13:182.
76. Anonymous. The WHO application of ICD – 10 to deaths during pregnancy, childbirth and the puerperium: ICD-MM 2012.
77. MRC Research Unit for Maternal and Infant Health Care Strategies PPIP Users and the Saving Babies Technical Task Team. Saving babies 2008–2009. Seventh report on perinatal care in South Africa. Available from: www.ppip.co.za.
78. Korteweg FJ, Gordijn SJ, Timmer A, Holm JP, Ravise JM, Erwich JJ. A placental cause of intra-uterine fetal death depends on the perinatal mortality classification system used. Placenta. 2008; 29:71–80.
79. Shrestha M, Shrestha L, Basnet S, Shrestha S. Trends in perinatal mortality in Tribhuvan University Teaching Hospital: 13 years review. J Nepal Paediatr Soc. 2012;32:150–3.
80. Singh A, Toppo A. Re. Co. De.: a better classification for determination of still births. J Obstet Gynaecol India. 2011;61: 656–8.
81. McClure EM, Nalubamba-Phiri M, Goldenberg RL. Stillbirth in developing countries. Int J Gynaecol Obstet. 2006;94:82–90.
82. Schmiegelow C, Minja D, Oesterholt M, Pehrson C, Suhrs HE, Boström S, et al. Factors associated with and causes of perinatal mortality in northeastern Tanzania. Acta Obstet Gynecol Scand. 2012;91:1061–8.
83. Stormdal BH, Varli H, Ingela A, Kublickas M, Papadogiannakis N, Pettersson K. Causes of stillbirth at different gestational ages in singleton pregnancies. Acta Obstet Gynecol Scand. 2014;93: 86–92.
84. Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. J Am Med Assoc. 2011;306: 2459–68.
85. Pattinson RC, Say L, Makin JD, Bastos MH. Critical incident audit and feedback to improve perinatal and maternal mortality and morbidity. Cochrane Database of Syst Rev. 2005;(4): CD002961.
86. Humphrey M, Colditz P, Flenady V, Whelan N. Maternal and perinatal mortality and morbidity in Queensland. 2013.
87. Oza S, Lawn JE, Hogan D, Mathers C, Cousens SN. Neonatal causes of death for 194 countries with distributions for early and late periods and trends from 2000–2012. http://www.who.int/gho/child_health/en/. Accessed 10 Apr 2014.
88. World Health Organization. Born too soon: the global action report on preterm birth. World Health Organization; 2012 [10 Oct 2014]; Available from: http://www.who.int/pmnch/media/news/2012/201204_borntoosoon-report.pdf.
89. Flenady V, Koopmans L, Middleton P, Froen FJ, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet. 2011; 377:1331–40.
90. Aminu M, Unkels R, Mdegela M, Utz B, Adaji S, Van den Broek N. Causes of and factors associated with stillbirth in low- and middle-income countries: a systematic literature review. BJOG. 2014;121:141–56.
91. Di Mario S, Say L, Lincetto O, Di Mario S, Say L, Lincetto O. Risk factors for stillbirth in developing countries: a systematic review of the literature. Sex Trans Dis. 2007;34:S11–21.
92. Luo ZC, Kierans WJ, Wilkins R, Liston RM, Mohamed J, Kramer MS. Disparities in birth outcomes by neighborhood income: temporal trends in rural and urban areas, British Columbia. Epidemiology. 2004;15:679–86.
93. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? Lancet. 2005;365:891–900.
94. Drysdale H, Ranasinha S, Kendall A, Knight M, Wallace EM. Ethnicity and the risk of late-pregnancy stillbirth. Med J Aust. 2012;197:278–81.
95. Mohsin M, Bauman AE, Jalaludin B. The influence of antenatal and maternal factors on stillbirths and neonatal deaths in New South Wales, Australia. J Biosoc Sci. 2006;38:643–57.
96. Luo ZC, Wilkins R, Luo Z-C, Wilkins R. Degree of rural isolation and birth outcomes. Paediatr Perinat Epidemiol. 2008;22:341–9.
97. Fretts RC. Etiology and prevention of stillbirth. Am J Obstet Gynecol. 2005;193:1923–35.
98. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. Lancet. 1987;1:1192–4.
99. Haavaldsen C, Sarfraz AA, Samuelsen SO, Eskild A. The impact of maternal age on fetal death: does length of gestation matter? Am J Obstet Gynecol. 2010;203:554.e1–8.
100. Reddy UM, Ko CW, Willinger M. Maternal age and the risk of stillbirth throughout pregnancy in the united states. Am J Obstet Gynecol. 2006;195:764–70.
101. Hogberg L, Cnattingius S. The influence of maternal smoking habits on the risk of subsequent stillbirth: is there a causal relation? BJOG. 2007;114:699–704.
102. Stephansson O, Dickman PW, Cnattingius S. The influence of interpregnancy interval on the subsequent risk of stillbirth and early neonatal death. Obstet Gynecol. 2003;102:101–8.
103. Anonymous. First Nations Regional Longitudinal Health Survey (RHS) 2002/03: results for adults youth and children living in first nations communities. Ottawa: Assembly of First Nations and the First Nations Information Governance Committee; 2007.
104. Chamberlain C, O'Mara-Eves A, Oliver S, Caird JR, Eades SJ, Thomas J. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev. 2013;10:CD001055.
105. Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. BJOG. 2007;114:243–52.
106. Aliyu MH, Wilson RE, Zoorob R, Chakrabarty S, Alio AP, Kirby RS, et al. Alcohol consumption during pregnancy and the risk of early stillbirth among singletons. Alcohol. 2008;42: 369–74.
107. Strandberg-Larsen K, Nielsen NR, Gronbaek M, Andersen PK, Olsen J, Andersen AM. Binge drinking in pregnancy and risk of fetal death. Obstet Gynecol. 2008;111:602–9.
108. Anonymous. Mater Mothers' Hospital clinical report, 2009; incorporating selected clinical outcomes for 2008. Brisbane: Mater Health Services; 2009.
109. Ray JG, Urquia ML. Risk of stillbirth at extremes of birth weight between 20 to 41 weeks gestation. J Perinatol. 2012;32:829–36.
110. Cnattingius S, Haglund B, Kramer MS. Differences in late fetal death rates in association with determinants of small for gestational age fetuses: population based cohort study. BMJ. 1998; 316:1483–7.
111. Bateman BT, Simpson LL. Higher rate of stillbirth at the extremes of reproductive age: a large nationwide sample of deliveries in the united states. Am J Obstet Gynecol. 2006;194:840–5.
112. Henningsen AA, Wennerholm UB, Gissler M, Romundstad LB, Nygren KG, Tiitinen A, et al. Risk of stillbirth and infant deaths after assisted reproductive technology: a Nordic study from the CoNARTaS group. Hum Reprod. 2014;29:1090–6.
113. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ. 2013;346:1–14.