PART I

Epidemiology and Scope of the Problem

CHAPTER 1
High Income Countries

Ruth Fretts, MD, MPH
Harvard Vanguard Medical Associates, Wellesley, MA, USA

Stillbirth and the definition "problem"

One of the difficulties in the study of stillbirth is that stillbirths are universally undercounted especially at lower ages of gestation. What constitutes a "stillbirth" varies considerably between countries, and while a universal definition has been desired, it is unlikely that a globally accepted definition will be agreed upon. The lower gestational age limit that divides a "miscarriage" from a "stillbirth" depends if a country has resources to collect information and if the intention of the data collection is to count the deaths that could possibly have "survived." In the United Kingdom, reporting of deaths begins at 24 weeks (presumably because the mortality of those born prior to 24 is so high); in most developing countries there is very little data about losses prior to 28 weeks of gestation.

The term fetal death, fetal demise, stillbirth, and stillborn all refer to the delivery of a fetus showing no signs of life. The World Health Organization (WHO) defines stillbirth as a "fetal death late in pregnancy" and allows each country to define the gestational age at which a fetal death is considered a stillbirth for reporting purposes [1]. A moderate proportion of countries have extrapolated from the WHO's definition of what constitutes the "perinatal period" to define stillbirth ($\geqslant$500 g, or if the weight is not known, with a gestational age greater than 22 completed weeks (154 days)). But even among developed countries the gestational age at which fetal losses are reported ranges from 16 weeks (The Netherlands) to 28 weeks (Sweden) [2]. Sweden recently revised their reporting laws because of pressures from parental advocacy groups and increasing numbers of live-born infants born prior to 28 weeks, but the stillborn counterparts were not included in national statistics. Other factors that influence the reported stillbirth rate are the accuracy of gestational age dating; whether obstetric providers are accurately educated on the definition of a "liveborn" or "stillborn"; if terminations of pregnancy for lethal or sublethal anomalies are specifically excluded; and if the inevitable previable spontaneous losses that results in a stillborn had labor augmented are included.

Within the United States, terminations of pregnancy for anomalies and augmented previable losses are specifically excluded from the stillbirth statistics but misclassification of these losses is common. Duke et al. compared fetal death reports to the reports generated from the active birth defects surveillance program in the Atlanta area. They found that 13% of fetal deaths should have been excluded from the fetal death statistics because the losses involved induction or augmentation of labor [3]. It is probable that providers recognize the intention of parents (the strong desire to have had a viable healthy pregnancy) and may fill out a fetal death report rather than report the loss as a termination of pregnancy or abortion.

In the United States, because the definition of stillbirth is determined by each state, there are significant variations which can substantially

Stillbirth: Prediction, Prevention and Management, First Edition. Catherine Y. Spong.

change the reported stillbirth rate by as much as 50% [4]. National reporting uses 20 weeks of gestation or 350 g if the gestational age is not known. The standardized definition for fetal mortality used by the U.S. National Center for Health Statistics (NCHS) is similar to the WHO definition but adds that a stillbirth must have "the absence of breathing, heart beats, pulsation of the umbilical cord, or definite movements of voluntary muscles" [5]. As advances in obstetrics occur both the neonatal and stillbirth rates decrease but the stillbirths less so, leaving stillbirth the largest contributor to perinatal mortality [6].

Scope of the problem

Compared to other health outcomes and the disease burden, the scope of stillbirth has been overlooked by many, including those who have the opportunity to prioritize spending for research and ultimately to devise and implement prevention strategies. In the United States, the chances that a pregnancy will end as a stillbirth is about 1/200 for white women and 1/87 for black women [7]. Stillbirth occurs more often than deaths due to AIDS and viral hepatitis combined; stillbirth is 10 times more common than sudden infant death syndrome, nearly 5 times more common than infant deaths related to congenital anomalies, and 5 times more often than postnatal deaths due to prematurity [8].

There are many downstream consequences of stillbirth, the most significant and long lasting being experienced by mothers. Women who experience stillbirth are at an increased risk of multiple maladies including depression, anxiety and posttraumatic stress disorder, somatization disorder, and family disorganization [9] (see Chapter 13).

The reason that the scope of the problem has been overlooked is multifactorial. Many people still consider stillbirths as "God's Will" and that death before birth counts less than those after, but for many parents a stillbirth represents loss of chance and a family member. Until recently goals for the reduction of stillbirth were not included as an important health indicator, yet stillbirths are a measurable "tip of the iceberg." Stillbirth rates reflect a woman's preconceptual health and nutrition status, her access to good care including contraception, first-trimester care, screening for infectious diseases and congenital anomalies, disease identification and management, and adequate care during labor which includes fetal monitoring, timely access to cesarean section and IV antibiotics.

Trends in stillbirth rates

The study of stillbirth trends in historical cohorts and among developing countries identifies factors that affect stillbirth rates and are therefore most amenable to change. Countries where longitudinal data on stillbirths are kept (Denmark, Sweden, Norway, England, and Wales among others), many stillbirth rates remained relatively stable from the 1900s until the early 1940s [10]. After this time period there began a significant decline which continued but then leveled out in the mid-1980s (Figure 1.1) [10]. Interestingly, the increasing focus on the study of stillbirth in the United Kingdom was thought to be a reflection on the decline of the fertility rate; J.A. Ryle, Professor of Social Medicine at Oxford, wrote in 1949 that there was a need to reduce stillbirths as they were a "wastage of human life" and "as a matter of national accountancy we can no longer afford to lose so many potential citizens" [10].

Vallgarda reviewed the characteristics of stillbirths that were 32 weeks of gestation or greater in Denmark from 1938 to 1947 and found that during this time period, stillbirths were reduced from 24.9 to 16.3/1,000 births (a 35% reduction). This correlated with a reduction in the numbers of women having births at home (reduced from 50% to 35% of births). In addition, in 1945, Denmark introduced a law that provided free antepartum care, which was widely used by women (70% of women initially attended prenatal care and by the 1960s this had risen to almost 100%). The types of stillbirths most noted to have decreased were those

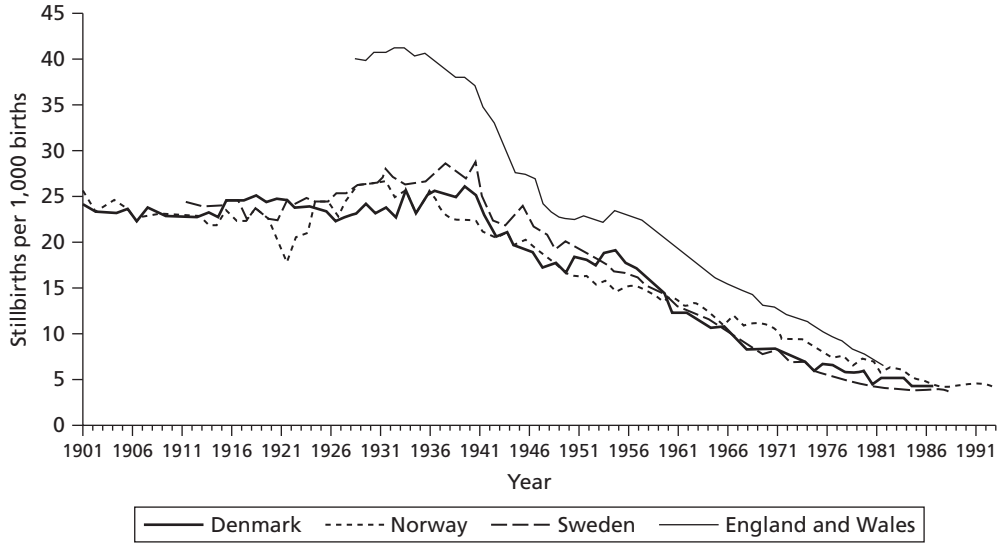

Figure 1.1 Stillbirth rates in Denmark, Norway, Sweden, and England/Wales, 1901–1990. (Data from Ref. [10].)

due to asphyxia in labor, malformations, bleeding, and disease of the mother [10].

Asphyxia in labor

In a Canadian hospital based study that evaluated specific causes of death of babies 20 weeks (or 500 g) or more over more than three decades, there were two causes of fetal death that were reduced by more than 95% (Figure 1.2) [11]. During the 1960s, intrapartum stillbirth was the third most common type of stillbirth (with those that were unexplained and related to growth restriction being more common). With the introduction of intrapartum monitoring and the availability of emergency cesarean section, the proportion of stillbirths that were due to asphyxia in labor dropped from 11% to 2% of total stillbirths with a rate of 0.2/1,000 births [11]. In general, intrapartum asphyxic deaths in term or near-term babies that occur more often than 1/1,000 births suggests a significant potential for improvements in quality of care in the labor and delivery unit [12, 13].

Rh iso-immunization

Stillbirth due to Rh iso-immunization has become a rare event in developed countries. In the same Canadian dataset that tracked changes in stillbirth over time, the authors noted a 95% reduction of these deaths during the study period of the 1960s to the early 1980s [11]. Initially Rhogam administration was given after the birth of an Rh-positive baby, and this helped reduced Rh iso-immunization considerably, but when the 28-week administration was introduced in the 1970s, the number of stillbirths were reduced even further making this now a very rare cause of stillbirth (less than 1/10,000 births) (Figure 1.2).

Congenital anomalies

The third cause of death that was notably reduced were those related to malformations. The rates of perinatal deaths due to congenital anomalies varies significantly based on maternal nutrition, environmental exposures, resources in the health systems, varied policies on screening for congenital anomalies, and the availability of terminations of pregnancy [12–15]. Within 10 European population-based cohorts for the MOSAIC study, 85% of terminations after 22 weeks of gestation were for congenital anomalies with 50% of these occurring between 22 and 23 weeks of gestation

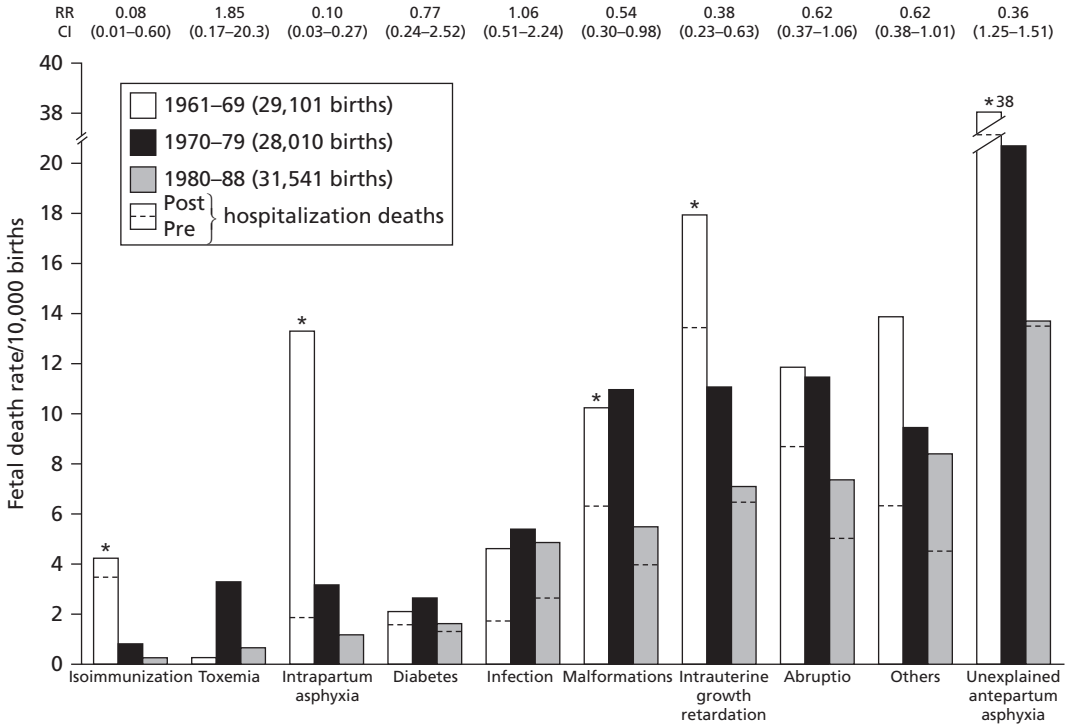

Figure 1.2 Specific causes of stillbirth during three decades in a Canadian hospital, both prior to and after hospitalization per 10,000 births. (Data from Ref. [11].)

and the rest later [15]. Exclusion of terminations of pregnancy reduced the reported stillbirth rate by half. Within the 10 European countries, the percent of stillbirths related to congenital anomalies varied significantly. In Poland where the policy for termination of pregnancies is quite restrictive, the proportion of stillbirths related to congenital anomalies was 34%, in the United Kingdom where the policies for terminations of pregnancy for congenital anomalies is more liberal, these deaths account for only 3.8% of stillbirths [14]. Obviously for parents a termination of pregnancy for congenital anomalies is a traumatic event, the pregnancy outcome however is not typically included in the stillbirth statistics [3, 14, 15].

Over the past 50 years in the United States there was an approximately 70% reduction of late losses (defined as 28 weeks or more), whereas there has been virtually no decrease in early losses (20–28 weeks), since the 1990s the decline has slowed with the number of early fetal deaths exceeding the number of late losses (Figure 1.3) [16]. Unfortunately, within the United States there has not been a large longitudinal study of the specific causes of stillbirth, but there is a large body of evidence which demonstrates that some types of stillbirths have been reduced when prevention strategies have been developed. A prerequisite to designing a prevention strategy however is a thorough stillbirth evaluation which is not routinely performed in the United States. The stillbirth evaluation includes placental and fetal pathology, selected laboratory evaluation, a narrative on what lead up to the diagnosis of stillbirth, including maternal medical and social risk factors, access to care, the quality of care (see Chapter 12–14).

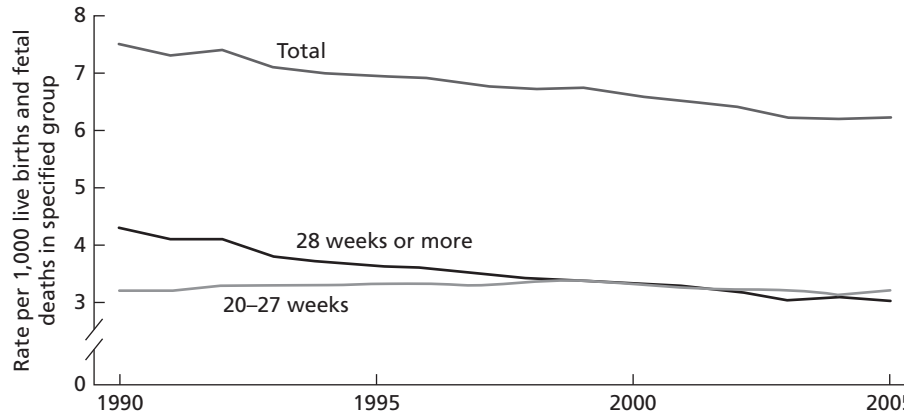

Figure 1.3 Fetal mortality rates by period of gestation: United States, 1990–2005. (Data from Ref. [4].)

Common causes of stillbirth

There has been considerable evolution on how the causes of stillbirth have been classified (see Chapter 3) and whether or not associated conditions are considered causes or risk factors for stillbirth. The severity of pathology whether it is within the placenta or in a disease state such as pregnancy-induced hypertension may be variably interpreted as a cause or as a contributor to the demise. There are notable differences in the types of stillbirth that occur at different gestational ages. Notwithstanding these issues, the most common types of stillbirth remain those that are "unexplained." Again the proportion of those that are left unexplained depends on the rigorousness of the stillbirth evaluation. Unexplained losses are those pregnancies that have not been complicated by fetal, maternal, or placental conditions and occur in an appropriately grown baby without evidence of infection or antepartum bleeding [17, 18]. The second and third most common causes of stillbirth are both related to problems related to placental function, with the difference being rated to the acuity of the pathology. Babies that are severely growth restricted (without evidence of chromosomal anomalies or perinatal infection) die presumably due to placental dysfunction [19]. This process is gradual enough that the baby's growth falls off of the expected growth curve and eventually succumbs (see Chapter 7). The third most common cause of fetal death is related to abruptio placenta. This is a more acute process, with the diagnosis made clinically in the setting where there is antepartum bleeding and premature separation of the placenta that is severe enough to cause a fetal demise.

Causes of stillbirth by gestational age

Spontaneous preterm losses from 20 to 24 weeks of gestation

This is one of the largest categories of loss that occur between 20 and 24 weeks. Reviews of these losses reveal an over-representation of black women, of multiple gestations, and a history of a pregnancy achieved using advanced reproductive technologies (Figure 1.4) [7, 20]. Depending on when a women presents for evaluation, she may be diagnosed with premature rupture of membranes, cervical incompetence, chorioamnionitis, antepartum bleeding with or without premature labor. While a fair number of women will also have a living fetus at the beginning of the birth process, very often the baby is born dead.

Stillbirths less than 28 weeks of gestation

Using the Canadian McGill Obstetrical and Neonatal Database, Fretts et al. evaluated the timing of specific causes of stillbirth. In their study,

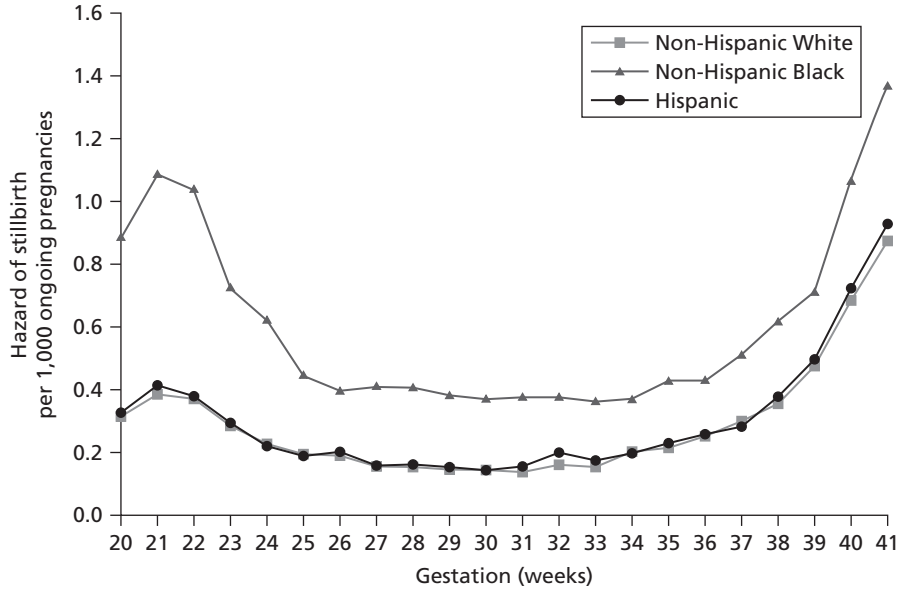

Figure 1.4 Fetal mortality rates by maternal age in singleton pregnancy and multiple pregnancies, 2005. (Data from Ref. [4].)

there was a 97% autopsy rate and a primary cause of death was assigned in the setting of a perinatal review committee [11]. In general, unless there was obvious and significant cord pathology so that a cord accident was the only logical explanation for stillbirth, those births that lose cord loops or knots noted were classified as unexplained.

These so-called "early fetal deaths" have been most difficult to influence with rates much unchanged over the past 30 years. The most common causes of death prior to 28 weeks of gestation include infection (19%), malformations (14%), abruptio placenta (14%), severe growth restriction (7%), and intrapartum asphyxia (7%). While for most of these deaths a cause of death can be assigned, about 20% were unexplained [11].

Stillbirths from 28 to 36 weeks

In the Canadian dataset between 28 and 36 weeks of gestation, unexplained stillbirths remained the most common type of demise (26%), the next most common type of stillbirth were those that occurred in babies with severe growth restriction (19%), followed by abruptio placenta (18%), infection (8%), malformations (8%), and maternal disease (6%) [11].

Stillbirths at and beyond 37 weeks of gestation

At term, the proportion of unexplained stillbirths increased to 40%, 14% died from severe growth restriction, 13% resulted from abruptio placenta, 8% from maternal disease, 16% were "other causes" including umbilical cord abnormalities, nonimmune hydrops and vasa previa, and twin-to-twin transfusion [11].

Unexplained stillbirths

An "unexplained stillbirth" is the most common type of stillbirth and in some ways are the most troubling. Typically these tend to occur late in pregnancy [17, 18]. Because the unexplained stillbirth is a diagnosis of exclusion, it is subject to the thoroughness of the stillbirth evaluation.

Incomplete examinations will underestimate the role of infection, chromosomal and congenital anomalies. Some classification systems exclude fetal deaths that occurred in the very growth-restricted fetus (less than the 3rd percentile or the 10th percentile) from those that are categorized as "unexplained" while others do not [19].

Where good data exists, late pregnancy (after 36–37 weeks of gestation), advanced maternal age (OR 3.3–5.1), and obesity (OR 2–3) are all risk factors for these unexplained deaths [17, 18]. There are several theories on why these late stillbirth occur but none have been proven and it is likely that the mechanisms of death are heterogenous. The observation that these deaths occur more often in older women late in pregnancy suggests diminished placental function [21, 22] (Figure 1.5). One preventive strategy in this setting is consider these pregnancies "postdates" sooner and follow either with antepartum testing or induction of labor prior to the typical "postdate" period. Theoretically the optimal timing of delivery could be modified according to the patients risk factors for stillbirth; unfortunately there have been no randomized controlled trial evaluating the risks and benefits of such approach that are powered to address stillbirth reduction. Nicholson et al. [23] did demonstrate that the strategy of the active management of risk while associated with a significantly elevated risk of induction of labor was not associated with an increased risk of cesarean section; they reported a lower risk of fetal adverse outcomes but this study was not powered to look at perinatal mortality.

Other researchers have evaluated the role of the inflammatory response in the unexplained stillbirth. In an ideal setting, if there is fetal hazard such as infection, lymphokines will initiate labor, thus "rescuing" the baby by birth. But the factors in the mother and the baby that are responsible for the initiation of labor are not well known. There are a proportion of late "explained" stillbirths that appear to be related to infection, but for some reason the mother's body did not mount the appropriate response to initiate labor prior to the baby's death [24].

The relationship between elevated blood pressure and stillbirth has been well described, but more recently some researchers have noted that relative hypotension may be a risk for stillbirth [25]. Warland et al. performed a matched case–control study of

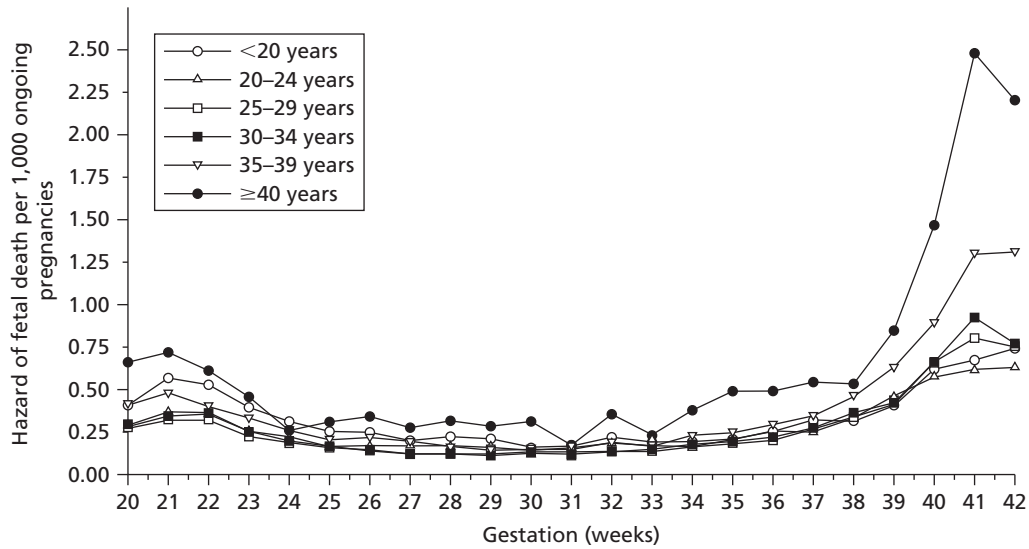

Figure 1.5 Maternal age and the risk of stillbirth throughout pregnancy in the United States hazard (risk) of stillbirth for singleton births without congenital anomalies by gestational age, 2001–2002. (Data from Ref. [22].)

124 women who had a stillbirth with 243 women who had a liveborn. Interestingly in their study, hypertension (systolic blood pressure of greater than or equal to 130 mmHg) was associated with a lower rate of stillbirth (RR 0.4, 95% CI 0.37–0.43), presumably this was due to increased pregnancy monitoring and appropriate induction. But they also found that women whose diastolic blood pressure fell in the borderline range 60–70 mmHg had an elevated risk over their normotensive controls (OR 1.8, 95% CI 1.1–3.0) [25]. While this relationship has not been a consistent finding in studies, it deserves further attention [26].

Placental dysfunction and fetal growth restriction

Approximately half of stillbirths have failed to reach their expected growth potential as measured by birthweight less than the 10th percentile (corrected for gestational age and parental characteristics) [27]. Preterm stillbirths are more likely to be small-for-gestational age and have other placental pathology such as abruptio placenta, although certainly growth restriction also occurs at term [12, 27]. The detection of growth restriction remains a major challenge since most stillbirths that are severely growth restricted were not recognized as growth restricted prior to the diagnosis of the stillbirth [13, 19]. When fetal growth restriction is detected antepartum and preterm, the overall perinatal mortality remains elevated because of the underlying placental pathology, the risk of iatrogenic preterm birth, and its related morbidity and mortality (see Chapter 7).

In the Confidential Enquiry of Stillbirths and Deaths in Infancy 2001, the most common finding in the review of stillbirths was the failure to detect fetal growth restriction; this was seen in 10% of stillbirths in their review. Other deficiencies of care involved the management for fetal growth restriction, the management of hypertension, deficiencies of the interpretation of fetal monitoring (3% for each), and the failure to adequately manage pregnancies complicated by decreased fetal movement [28].

Abruptio placenta

Premature separation of the placenta is the third most common cause of stillbirth. Fatal abruption is more common in the preterm fetus and is strongly associated with placental problems and inflammation [29]. The rates of abruption appear to be increasing in the United States and elsewhere. Maternal drug use is the strongest association among the maternal risk factors, but there are other important risk factors, such as smoking, hypertension, and preeclampsia. Cessation of smoking and drug use are important strategies, and past drug use should be gathered as part of the obstetric history [13]. Also, women who report second- and third-trimester bleeding need to be considered "high risk," and have appropriate fetal monitoring, including periodic assessments of fetal growth.

Infection

The rates of stillbirths due to infection in high resource settings have been relatively unchanged over the past number of decades (Figure 1.2), most of these have occurred in early stillbirths (20–28 weeks) [11]. A substantial proportion of these deaths are related to bacterial ascending infections with *Escherichia coli*, group B streptococci, and *Ureaplasma urealiticum* [30]. When viruses are looked for with polymerase chain reaction (PCR), a moderate number of stillbirths will have placental tissue that is positive for cytomegalovirus (CMV), herpes simplex virus (HSV), or Parvovirus 19. In a study of 96 stillbirths and 35 healthy full-term controls, 33% of stillbirths had positive placental evidence for viruses (16% CMV, 13% Parvovirus 19, 5% HSV), whereas only 6% of healthy controls had placental tissue that was positive. Findings at autopsy such as fetal hydrops and chronic villitis were strongly associated with positive PCR testing [31] (see Chapter 5).

Cord accidents

The study of cord accidents has been difficult because at the birth of a stillborn baby careful

systematic evaluation of the cord is not usually carried out. We know that about one-third of live-born babies have one or more cords wrapped around his or her neck. With a live baby this is considered an incidental finding, but it is difficult to determine in the setting of a stillbirth if cord pathology is the *cause* of the death or an incidental finding. Because whether a stillbirth has been related to a cord accident is subjective, there has been considerable variation on the proportion of stillbirths that are attributed to stillbirth, but on average, 20% of stillbirths are attributed to cord accidents by physicians (see Chapter 10). Until we know more, it is important that when a stillborn baby is delivered with the presence of a cord-related issue (cord loops, knots, torsion, knotting, or entanglement) a thorough evaluation of baby, mother, placenta, and cord be conducted in order to determine if there were other factors or conditions that could have contributed to the stillbirth. Some have recommended evaluation of the cord location by ultrasound after the diagnosis of stillbirth is made so the number or cord loops can be assessed. Photographs taken just after are also useful because they can be viewed during a perinatal review and placed in context with other pathological findings. These would be important steps in the study of cord accidents and make this diagnosis more systematic and less subjective.

Multiple gestations

Over the past two decades, U.S. rates of twin pregnancies have more than doubled and higher-order multiples have increased 6- to 12-fold [20, 33]. The increasing number of multiples is due to increased use of assisted reproductive technologies and an increasing proportion of older mothers (Figure 1.6). The stillbirth rate among multiples is fourfold higher than singletons (19.6/100 vs. 4.7/1,000) [32]. The higher rates are due to both complications specific to multiple pregnancies (such as twin-to-twin transfusion syndrome) and increased risks of complications common to singletons and multiples, in particular fetal abnormalities and growth restriction. Triplet or higher numbers of gestations are at high risk for multiple complications, including preterm birth and the death of one or more of the babies. Among twin gestations, it is recommended that fetal growth be monitored periodically, and even in uneventful twin pregnancies, delivery is recommended by 39 weeks because of late unanticipated stillbirths [33]. Higher order multiples are associated with even higher rates of perinatal death. One important strategy to reduce stillbirth may be to reduce the number of embryos transferred during an induced reproductive cycle to reduce the number of multiple gestations [20].

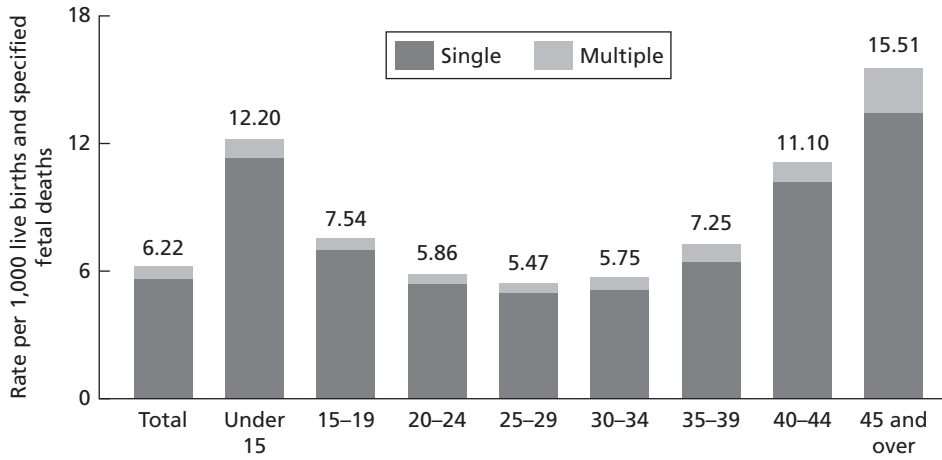

Figure 1.6 The hazard of stillbirth per 1,000 ongoing pregnancies for non-Hispanic white, non-Hispanic black, and Hispanic women. (Data from Ref. [7].)

Maternal risk factors for stillbirth

Risk factors for stillbirth are the same in both developed and developing countries, but the prevalence of these risk factors varies significantly. Unrecognized and uncontrolled hypertension or diabetes, lack of prenatal care, the lack of access to timely cesarean delivery are risk factors everywhere, but this occurs much less often in developed countries. In developed countries, hypertension and diabetes are the most common medical conditions in pregnancy [34] (see Chapter 8). Common social risk factors are obesity, smoking, low maternal education, and first birth (Table 1.1). Extremes in maternal age are risk factors for stillbirth (Figure 1.5). In developed countries, older women over the age are more likely to be starting a family.

Maternal age and parity

In most countries there is a U-shaped relationship between maternal age and stillbirth (Figure 1.5) [4]. Older maternal age is an independent risk factor for stillbirth even after controlling for factors that occur more often in older women, such as obesity,

Table 1.1 Common risk factors for stillbirth in the United States.

Risk factor	Prevalence (%)	Odds ratio
Obesity		
BMI 25–29.9	21–24	1.4–2.7
BMI >30	20–34	2.1–2.8
Nulliparity compared to second pregnancy	40	1.2–1.6
Fourth child or greater compared to second	11	2.2–2.3
Maternal age		
35–39	15–18	1.8–2.2
40+	2	1.8–3.3
Multiple gestation		
Twins	2.70	1.0–2.2
Triplets or greater	0.14	2.8–3.7
Advanced reproductive technologies (all)	1–3	1.2–3.0
Smoking	10–20	1.7–3.0
Alcohol use (any)	6–10	1.2–1.7
Illicit drug use	2–4	1.2–3.0
Low education/socioeconomics status	30	2.0–7.0
Antenatal visits <4*	6	2.7
Black (reference white)	15	20–2.2
Hypertension	6–10	1.5–4.0
Diabetes	2–5	1.5–3.0
Large for gestational age >97% without diabetes	12	2.4
Fetal growth restriction		
<3%	3.00	4.8
3–10%	7.50	2.8
Previous growth-restricted infant	6.70	2.0–4.6
Previous preterm birth with growth restriction	2	4.0–8.0
Decreased fetal movement	4–8	4.0–12.0
Previous stillbirth	0.50	2.0–10.0
Previous cesarean section	22–25	1.0–1.5
Postterm pregnancy (>42 weeks) compared to 38–40 weeks	6	2.0–4.0

Data from Ref. [35].
*Stillbirth 37 weeks or greater.

gestational diabetes, hypertension, and multiple gestations [21]. Advanced maternal age also interacts negatively with first birth, smoking and black rate to further increase the risk of stillbirth. Similar to maternal age, maternal parity (first birth and high parity) are risk factors for stillbirth. Women in the United States having their fourth child (or greater) experience 2.3 times the risk of stillbirth when compared to a woman having her second child [36].

Previous obstetric history

A prior adverse obstetric outcome, such as a preterm birth (spontaneous or induced for medical reasons) or delivery of a growth-restricted infant have common etiological factors to those pregnancies that end in stillbirth. In terms of placental pathology, stillbirth is on the spectrum of disease; a history of a baby being born both very preterm and growth restricted confers a higher risk of subsequent stillbirth than a history of a term stillbirth that was well grown [37] (Table 1.1).

The role of a previous cesarean delivery on the future risk of stillbirth is unclear at present with different risk estimates seen in different populations [38, 39]. It is not certain if the scarring from cesarean delivery reduces placental reserve increasing the risk of a subsequent stillbirth or if having a primary cesarean is a marker of underlying pathology.

Obesity

Obesity is a modifiable risk factor for stillbirth. In developed countries, modern society is "obesogenic"; this is related to a more sedentary lifestyle and the easy access to calorie-rich foods. In the United States, the National Health and Nutrition Examination Survey (NHANES) estimates of obesity (BMI of $\geqslant$30) rose from 14% in adults 20 years of age or older in the early 1960s to 34% in 2005. Extreme obesity (BMI of 40.0 or greater) rose from 1% to 5.7% in the same time period [40]. Prepregnancy obesity is associated with a 3.5- to 4.6-fold increased risk for stillbirth after 37 weeks of gestation [41, 42]. The reason for this increased risk is not known, but placental dysfunction, sleep apnea, metabolic abnormalities, and inability to easily monitor fetal growth or fetal movement are proposed mechanisms [32].

Preconception care

Access to contraception, screening for sexually transmitted diseases, optimizing maternal weight and health, prenatal folic acid supplementation, optimal spacing of pregnancies, all have measurable effects on pregnancy outcome, and stillbirth. It would be an oversight not to recognize the above opportunities for improved health and are likely to have a substantial effect on stillbirth rates.

Alcohol, drug use, smoking and stillbirth

The use of alcohol, illicit drug use, and smoking all have known adverse pregnancy effects; these effects are worse with multiple substance use. Taking the opportunity to counsel and support women to reduce these risky behaviors can improve pregnancy outcomes, although resuming substance use after pregnancy is common. Underreporting of substance abuse is common. Smoking is a common and modifiable risk factor for stillbirth. While prospective studies of smoking cessation interventions are generally underpowered to detect a reduction in stillbirth, consistent epidemiological data supports the conclusion that smoking is associated with preterm birth, fetal growth restriction, and stillbirth, and smoking cessation remains a simple and straightforward stillbirth prevention strategy [43].

Racial factors and stillbirth

There are many social determinants that affect the health of women and her baby, so it can be difficult to tease out what might be primarily biological risk factors within a racial group, from the racial disparities in economic status, health, literacy, and immigration status. A study of more than five million American births demonstrated that black

women had more than twice the rate of stillbirth (11.6/1,000) when compared to white (4.9/1,000) or Hispanic women (5.5/1,000) [7]. While education conferred a 30% reduction in stillbirth risk for white women who had more than 12 years of education, there was only a 9% reduction seen for black women and a 4% reduction for Hispanic women (which was not statistically significant) [7]. Black women who experienced a stillbirth were also more likely to have experienced medical, obstetrical, or labor complications than white and Hispanic women (30.1%, 19.5%, and 19.3%, respectively). While black women had higher rates of stillbirth throughout pregnancy than white and Hispanic women (Figure 1.4), this was greatest at 20–23 weeks of gestation (relative risk of hazard) for black compared to white women (RR 2.7 95% CI 2.6–2.9), but an increase was also seen late in pregnancy (>40 weeks, RR 2.2, 95% CI 2.1–2.3) [7].

Evaluating the reasons for these differences both in early and late stillbirths would provide important insight into the chain of events, and mechanisms of loss. One suspects that there may be biological reasons for early losses specifically for black women Since these women are more likely to have uterine fibroids than white women and fibroids are associated with pregnancy complications do influence the risk of stillbirth. In the United States, black women are less likely to undergo an induction of labor after 40 weeks than white women [7].

Decreased fetal movements

Approximately 4–10% of women will report decreased fetal movements sometime during their pregnancy [44, 45]. While most pregnancies will have a normal outcome, recent studies estimate that approximately one quarter of pregnancies will have a less than optimal outcome (growth restriction 14–23% and stillbirth 1.5–4.3%) [45]. Women who presented more than once with this complaint, who had had a history of obstetric problems and who had a fundal height smaller than expected had the worst outcome with a relative risk of 22 for experiencing a poor obstetric outcome [45]. Certainly the management of this complaint is an area of significant opportunity for stillbirth reduction. In a study where information was given to patients at their 18-week appointment and providers were given clinical guidelines for the management of decreased fetal movement (including a timely evaluation of fetal wellbeing with both a nonstress test and an assessment of fetal growth with ultrasound), a 33% reduction of stillbirths was found in 14 delivery units in Norway [44]. During this study period, the number of women who waited 48 h or more prior to contacting her provider was reduced from 54% to 49%, and the number of women who received an ultrasound during the course of her evaluation rose from 86% to 94% [44]. While it is not known which aspect of this intervention had the greatest benefit for stillbirth reduction, it is obvious studying stillbirth and the management of high-risk conditions is likely to have a significant benefit on stillbirth rates.

Suboptimal care

In developed countries, the failure to detect severe fetal growth restriction is the most common "missed" opportunity in audits of perinatal mortality after 28 weeks of gestation (estimates range from 6.2% to 14% in the European working group). Maternal smoking (and perinatal mortality related to growth restriction and placental pathology) was noted in 6–21% of cases [13]. The management of hypertension, deficiencies of the interpretation of fetal monitoring during labor and delivery, and the failure to adequately manage pregnancies complicated by decreased fetal movement were also areas where there was reasonable evidence that had the factor been appropriately managed, that a fatal outcome could have been avoided [28, 46].

Strategies for prevention

Until recently, stillbirths have been understudied, but if the outcome of a stillbirth is viewed as the "tip of the iceberg" many improvements in obstetric care can be generated (Table 1.2, Figure 1.7). Strategies for stillbirth prevention begin with a

Table 1.2 Strategies for stillbirth prevention in high income countries.

Improve the systematic review and evaluation of stillbirths similar to other sentinel events
Develop a "stillbirth package" which includes the optimal stillbirth evaluation and support materials for the parents
Improve access and quality of obstetric care for minorities, recent immigrants, poor- and less-educated women
Offer screening for congenital/karyotypic anomalies with the availability of termination of pregnancy
Promote healthy habits with smoking cessation and optimizing weight before pregnancy
Reduction of multiple gestations by reducing the number of embryos transferred in the reproductive technologies
Improve strategies for the detection and management of fetal growth restriction
Optimize the management of decreased fetal movement in the preterm and term pregnancies
Improve management of high-risk conditions with the use of a high-risk roster, develop outreach for noncompliant patients
Adopt evidence-based algorithms monitoring high-risk pregnancies

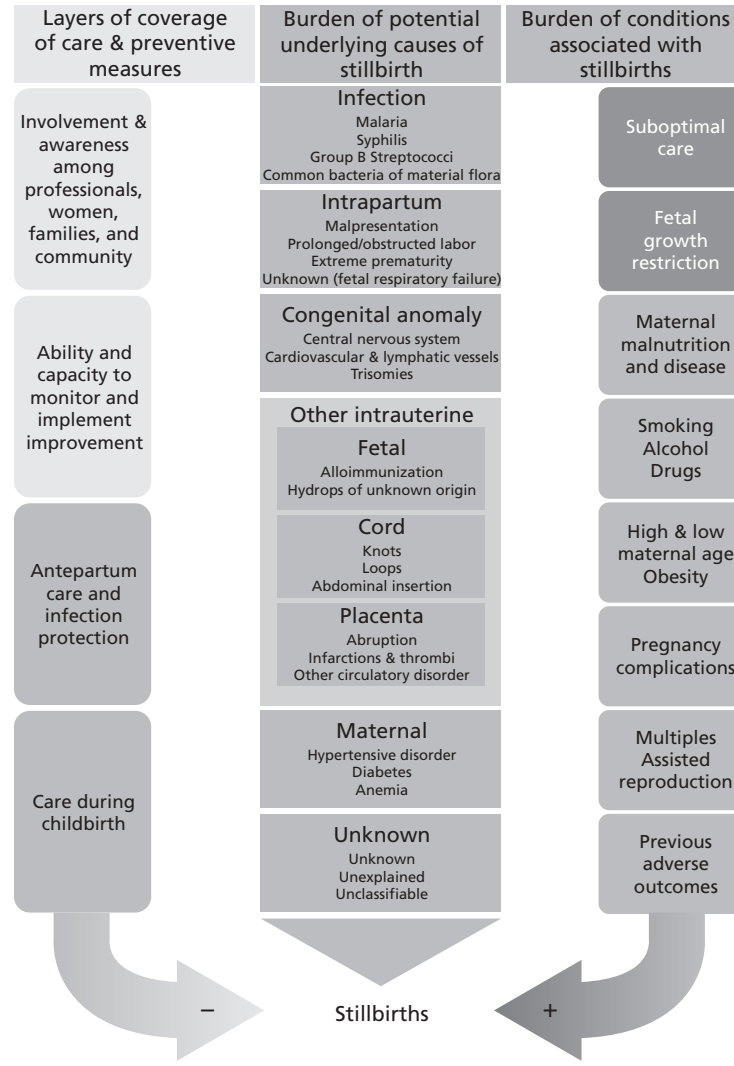

Figure 1.7 Stillbirth determinants. A framework of the setting and conditions that constitute the data sources needed for the understanding of stillbirth mortality. The classification of significant proportions of underlying causes of death globally is reproduced from CODAC. (Reproduced from Ref. [47], with permission from Biomed Central.)

systematic evaluation of each case, which includes the review of medical, obstetric, and social risk factors. A systematic evaluation often leads to the identification of areas of "opportunity." Late prenatal care may result in poor obstetric dating, and a missed opportunity for prenatal diagnosis and an improvement in healthy habits. If there are too many early losses related to higher-order multiple gestations, then feedback to the infertility providers may reduce the number of embryos that are transferred.

There are often opportunities to improved documentation so that the patient and her provider can develop a strategy for antepartum monitoring if a future pregnancy is planned. A more thorough stillbirth evaluation will help assess the risk of recurrence (see Chapter 12). Obstetric providers and labor room nurses need to be educated on the cultural barriers to obtaining autopsy; many parental concerns can be addressed by accommodating and respecting the patient's beliefs while also maximizing the opportunities to find a cause or contributor to the stillbirth.

Improved roster systems for high-risk patients will improve outreach for noncompliant or disorganized patients, thus improving the detection of worsening fetal or maternal status. Improved evidence-based algorithms for high-risk conditions will facilitate care (i.e., delivering twin gestations prior to the estimated due date) [33]. Until recently the management of decreased fetal movement involved only the assessment of imminent fetal jeopardy (with a nonstress test) but missed the opportunity to review other potential risk factors and the opportunity to assess fetal growth. Development of a "stillbirth package" which includes information and support for both the provider and the patient will help facilitate care during this stressful time.

References

1. World Health Organization. Definitions and indicators in Family Planning Maternal & Child Health and Reproductive Health. Geneva: WHO Press; 2001.
2. Gordijn SJ, Korteweg FJ, Erwich JJHM, et al. A multilayered approach to the analysis of perinatal mortality using different classification systems. Eur J Obstet Gynecol Reprod Biol 2009;144:99–104.
3. Duke W, Williams L, Correa A. Using active birth defect surveillance programs to supplement data on fetal death reports: improving surveillance data on stillbirths. Birth Defects Res 2008;82:799–804.
4. MacDorman MF, Kirmeyer S. The challenge of fetal mortality. NCHS data brief, no 16. Hyattsville, MD: National Center for Health Statistics; 2009.
5. National Center for Health Statistics. State Definitions and reporting for live births, fetal deaths, and induced terminations of pregnancy. Revision. Hyattsville, MD: NCHS; 1997.
6. World Health Organization. Neonatal and perinatal mortality. Country, regional and global estimates. Geneva: WHO Press; 2006.
7. Willinger M, Chia-Wen K, Reddy UM. Racial disparities in stillbirth across gestation in the United States. Am J Obstet Gynecol 2009;201:469e.1–8.
8. Kung HS, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. National Vital Statistics Report 56, Number 10; 2008.
9. Cacciatore J, Schnebly S, Froen JF. The effects of social support on maternal anxiety and depression after stillbirth. Health Social Care Community 2009;17:167–76.
10. Vallgarda S. Why did the stillbirth rate decline in Denmark after 1940? Popul Stud. Accessed 12 May 2010, 1–14, iFirst Styovlr, link to article 10.1080/00324721003746484.
11. Fretts RC, Boyd M, Usher RH, Usher HA. The changing pattern of fetal death 1961–1988. Obstet Gynecol 1992;79:35–9.
12. Bell R, Glinianaia SV, Rankin J, et al. Changing patterns of perinatal death, 1982–2000: a retrospective cohort study. Arch Dis Child Fetal Neonatal Ed 2004;89:F531–6.
13. Richardus JH, Graafmans WC, Verloove-Vanhorick P, Mackenback JP, the EuroNatal International Audit Panel, the Euronatal Working Group. Differences in perinatal mortality and suboptimal care between 10 European regions: results of an international audit. BJOG 2003;110:97–105.
14. Papiernik E, Zeitlin J, Delmas D, et al. Termination of pregnancy among very preterm births and its impact on the very preterm mortality: results from 10 European population-based cohorts in the MOSAIC study. BJOG 2008;115:361–8.

15. Boyd PA, DeVigan C, Khoshnood B, et al. Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. BJOG 2008;115:689–96.
16. MacDorman MF, Munson ML, Kirmeyer S. Fetal and perinatal mortality United States 2004. National Vital Statistics Reports 56; 2007.
17. Huang DY, Usher RH, Kramer MS, et al. Determinants of unexplained antepartum fetal deaths. Obstet Gynecol 2000;95:215–21.
18. Froen JF, Arnestad M, Frey K, et al. Risk factors for sudden intrauterine unexplained death: epidemiological characteristics if singleton cases in Oslo Norway, 1986–1995. Am J Obstet Gynecol 2001;184:694–702.
19. Froen JF, Gardosi JO, Thurmann A, et al. Restricted fetal growth in sudden intrauterine unexplained death. Acta Obstet Gynecol Scand 2004;83:801–7.
20. Salihu HS, Aliyu MH, Rouse DJ, et al. Potentially preventable excess mortality among higher-order multiples. Obstet Gynecol 2003;102:679–84.
21. Fretts RC, Schmittdiel J, Mclean FH, et al. Increased maternal age and the risk of fetal death. N Engl J Med 1995;333:953–7.
22. Reddy UM, Chia-Wen KO, Willinger M. Maternal age and risk of stillbirth throughout pregnancy in the United States. Am J Obstet Gynecol 2006;195:764–70.
23. Nicholson JM, Stenson MH, Kellar LS, et al. Active management of risk in nulliparous pregnancy at term, association between a higher preventive labor induction rate and improved birth outcomes. Am J Obstet Gynecol 2009;200:254.e1–13.
24. Lahra MM, Gordon A, Jeffery HE. Chorioamnionitis and fetal response in stillbirth. Am J Obstet Gynecol 2007;196:229.e1–e4.
25. Warland J, McCutcheon H, Baghurst P. Maternal blood pressure in pregnancy and stillbirth: a case control study of third trimester stillbirth. Am J Perinatol 2008;25:311–17.
26. Chen A, Basso O. Does low maternal blood pressure during pregnancy increase the risk of perinatal death? Epidemiology 2007;18:619–22.
27. Gardosi JO. Prematurity and fetal growth restriction. Early Hum Dev 2005;81:43–49.
28. Confidential enquiry into stillbirths and deaths in infancy 2001 in Northern Ireland. Maternal and Child Health Research Consortium, Eight Annual Report, London; 2001.
29. Oyelese Y, Ananth CV. Placental abruption. Am J Obstet Gynecol 2006;108:1005–16.
30. Goldenberg RL, Thompson C. The infectious origins of stillbirth. Am J Obstet Gynecol 2003;189: 861–73.
31. Syridou G, Spanakis N, Konstantinidou A, et al. Detection of cytomegalovirus, parvovirus B19 and herpes simplex viruses in cases of intrauterine fetal death: association with pathological findings. J Med Virol 2008;80:1776–92.
32. Smith GCS, Fretts RC. Stillbirth. Lancet 2007;370: 1715–25.
33. Robinson J, Healy B, Beatty T, Cohen A. The optimal gestational age for twin delivery. Am J Obstet Gynecol 2005;193:S183.
34. Simpson LL. Maternal medical disease: risk of antepartum fetal death. Semin Perinatol 2002;26:42–50.
35. Fretts RC. Stillbirth epidemiology, risk factors and opportunities for stillbirth prevention. Clinical Obstet Gynecol 2010;3:588–596.
36. Aliyu MH, Salihu HM, Keith LG, et al. Extreme parity and the risk of stillbirth. Obstet Gynecol 2005;106:446–53.
37. Surkan PJ, Stephansson O, Dickman PW, Cnattingius S. Previous preterm and small-for-gestational-age births and the subsequent risk of stillbirth. N Engl J Med 2004;350:777–85.
38. Smith CS, Pell JP, Dobbie R. Cesarean section and the risk of unexplained stillbirth in a subsequent pregnancy. Lancet 2003;362:1779–84.
39. Bahtiyar MO, Julien S, Robinson JN, et al. Prior cesarean delivery is not associated with an increased risk of stillbirth in a subsequent pregnancy: analysis of U.S. perinatal mortality data, 1995–1997. Am J Obstet Gynecol 2006;195:1373–8.
40. Flegal KM, Carroll ND, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA 2010;303:235–41.
41. Chu SY, Kim SY, Lau J, et al. Maternal obesity and the risk of stillbirth: a metaanalysis. Am J Obstet Gynecol 2007;197:223–8.
42. Nohr EA, Bech BH, Davies MJ, et al. Prepregnancy obesity and fetal death: a study within the Danish national Birth Cohort. Obstet Gynecol 2005; 106:250–9.
43. Salihu HM, Wilson RE. Epidemiology of prenatal smoking and perinatal outcomes. Early Hum Dev 2007;83;713–29.
44. Holm Tveit JV, Saastad E, Stray-Peterson B, et al. Reduction of late stillbirth with the introduction

of fetal movement information and guidelines—a clinical quality improvement. BMC Pregnancy Childbirth 2009;32:2–11.

45. O'Sullivan O, Stephen G, Martindale E, Heazell AEP. Prediction poor perinatal outcome in women who present with decreased fetal movements. J Obstet Gynecol 2009;29:705–10.
46. Saastad E, Vangen S, Froen JF. Suboptimal care in stillbirths—a retrospective audit study. Acta Obstet Gynecol 2007;86:444–50.
47. Froen JF, Gordjin SA, Abel-Allem, et al. Making stillbirth count, making numbers talk-issues in data collection for stillbirths. BMC Pregnancy Childbirth 2009;9:58, doi:10.1186/1471-2393-9-58.