



REVIEW ARTICLE

# Etiology and prevention of stillbirth

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## KEY WORDS

Stillbirth  
Fetal death  
Prevention  
Risk factors

**Objective:** This is a systematic review of the literature on the causes of stillbirth and clinical opinion regarding strategies for its prevention.

**Study design:** We reviewed the causes of stillbirth by performing a Medline search limited to articles in English published in core clinical journals from January 1, 1995, to January 1, 2005. Articles before this date were included if they added historical information relevant to the topic. A total of 1445 articles obtained, 113 were the basis of this review and chosen based on the criterion that stillbirth or fetal death was central to the article.

**Results:** Fifteen risk factors for stillbirths were identified and the prevalence of these conditions and associated risks are presented. The most prevalent risk factors for stillbirth are prepregnancy obesity, socioeconomic factors, and advanced maternal age. Biologic markers associated with increased stillbirth risk are also reviewed, and strategies for its prevention identified.

**Conclusion:** Identification of risk factors for stillbirth assists the clinician in performing a risk assessment for each patient. Unexplained stillbirths and stillbirths related to growth restriction are the 2 categories of death that contribute the most to late fetal losses. Late pregnancy is associated with an increasing risk of stillbirth, and clinicians should have a low threshold to evaluate fetal growth. The value of antepartum testing is related to the underlying risk of stillbirth and, although the strategy of antepartum testing in patients with increased risk will decrease the risk of late fetal loss, it is of necessity associated with higher intervention rates.

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## Methods

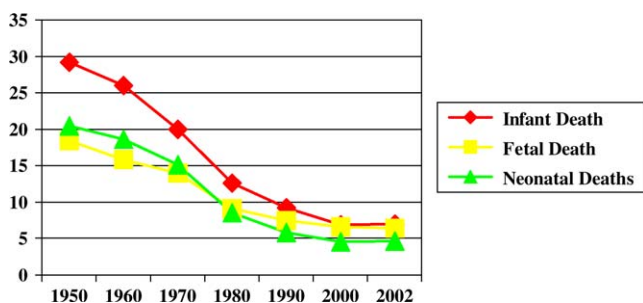
A Medline search was used with the MeSh terms “etiology,” “causality,” “pregnancy outcome,” “fetal death,” “stillbirth,” as was limited to human subjects, English articles with abstracts in core clinical journals from January 1, 1995, to January 1, 2005, identified 1445 papers. Articles were chosen if they had sufficient statistical power to address the risk factor of interest and

were performed in developed countries. A total of 113 were identified with this search and an additional 9 were cited for their historical information.

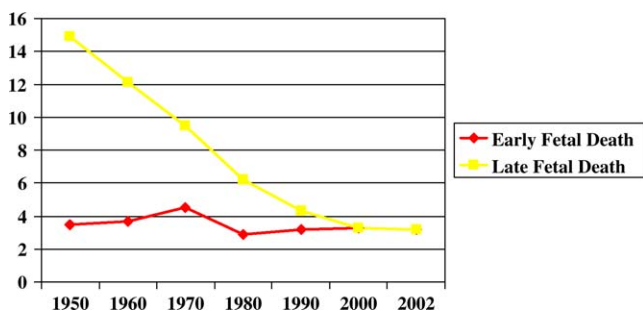
## Scope of the problem

Although stillbirth is infrequent, it occurs 10 times more often than sudden infant death.<sup>1</sup> In the United States, stillbirth accounts for a large proportion of all perinatal losses, although its causes remain incompletely understood. In developing nations, preterm births and stillbirths are grossly underreported, thus making international comparisons difficult. Even in developed nations, there is considerable variability in the threshold

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**Figure 1** Infant death rates, fetal death rates, and neonatal death rates.<sup>6</sup>



**Figure 2** Early (20-28 weeks of gestation) and late (29+ weeks of gestation) fetal deaths.<sup>6</sup>

for reporting stillbirth. These include differences in either the length of gestation or the birth weight.<sup>2-4</sup> The World Health Organization (WHO) classification of stillbirth is defined as fetal loss in pregnancies beyond 20 weeks of gestation, or, if the gestational age is not known, a birth weight of 500 g or more, which corresponds to 22 weeks of gestation in a normally developing fetus.<sup>5</sup>

In the United States during 2002, there were approximately 26,000 stillbirths, a rate of 6.4/1,000 total births. There also were about 28,000 infant deaths (equaling a rate of 7.0/1,000 live births), and 19,000 neonatal deaths (4.7/1,000 live births).<sup>6</sup> Black women have more than twice the rate of stillbirth of white women and, although some of this increased risk can be attributed both to access to, and quality of, medical care, other factors probably play a role as well.<sup>6-8</sup> Within the United States, there is no national program of review for these losses. Death certificates are filled out by the delivering clinician typically before autopsy and other data relevant to the stillbirth evaluation are available. Also, there is no international consensus on the classification of perinatal loss.

Since the 1950s, there has been a decline in rate of stillbirth, but it has not declined to the same extent as the neonatal death rate (Figure 1). Indeed, recent data from the United Kingdom show that there has been a slight increase in the stillbirth rate, related perhaps to the growing number of pregnancies in older women, as well as to increased numbers of multiple pregnancies,

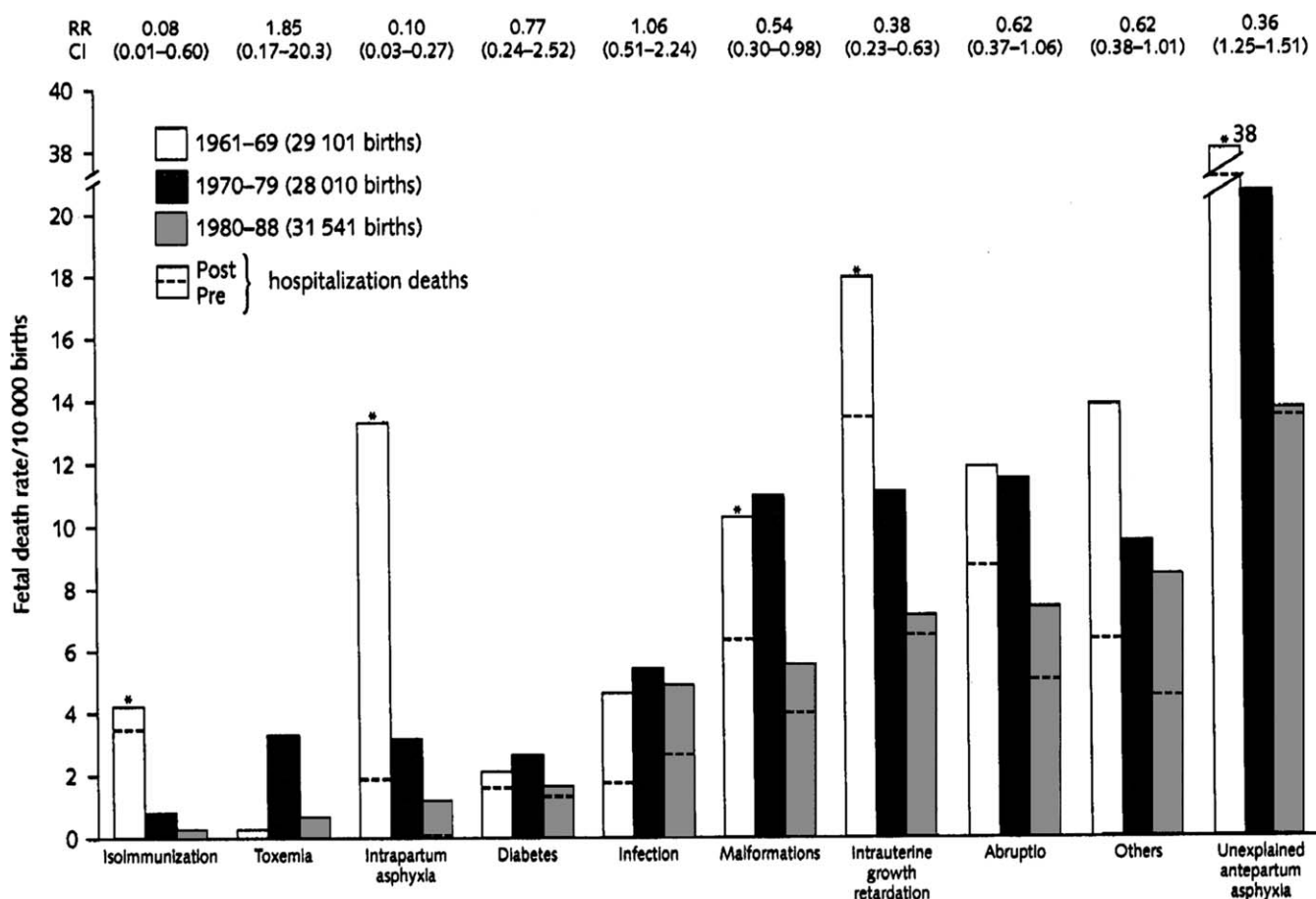
due in large part to an increase in assisted reproduction techniques.<sup>9</sup>

In large databases, fetal death is stratified by gestational age into early losses (ie, 20-28 weeks) and late fetal death (29 weeks or more; Figure 2).<sup>6</sup> Presumably, this approach was used initially to divide those pregnancies that might be salvageable (ie, late losses), from very early term losses, the majority of which would not be salvageable. Recent advances in neonatal care make this distinction somewhat arbitrary, but the causes of fetal death do vary according to gestational age.<sup>10</sup> The prevention of early fetal losses, in which a large proportion is related to infection, has been the most difficult to impact to date.<sup>10</sup> Ideally, of course, stillbirths deserve the same systematic evaluation as sudden infant deaths. If an obvious cause of death is not found, then by exclusion the stillbirth is usually considered “unexplained.” Only when fetal deaths are reported according to the specific causes of fetal demise can appropriate strategies be designed to reduce these losses.

## Causes of stillbirth

One of the largest and most comprehensive analyses of the causes of fetal death has been compiled and reported with the use of a Canadian database maintained at McGill University.<sup>10</sup> This analysis evaluated 709 stillbirths among 88,651 births with a 97% autopsy rate. This study was able to track changes in the specific causes of stillbirth over 3 decades (Figure 3). Since the 1960s, when the database was created, the greatest reductions in stillbirth occurred when strategies were developed to intervene in specific causes of fetal demise. Since the introduction of Rh immune prophylaxis, for example, there has been a 95% reduction in stillbirths because of Rh isoimmunization. Stillbirths during labor (intrapartum asphyxia) also decreased by 95% after the introduction of intrapartum monitoring (Figure 3). Currently, these causes of stillbirth account for less than 1 fetal death per 10,000 births. Higher rates of intrapartum asphyxia in fetuses weighing more than 2.5 kg suggests deficiencies in obstetric quality of care.<sup>11,12</sup> Interestingly, in the McGill experience throughout the 30-year study period, there was a low rate of stillbirths among women who had preeclampsia or diabetes (ie, less than 2/10,000), due in large part to aggressive management of these conditions.

Among other causes of stillbirth, the small-for-gestational-age (SGA) (ie, <2.4th percentile) fetus had an incidence of stillbirth of 46.8 per 1000, whereas the appropriate-for-gestational-age fetus had a rate of 4.0 per 1000 (odds ratio [OR] = 11.8; 95% CI 8.1-17.1).<sup>10</sup> The identification and appropriate management of the growth-restricted fetus remains a significant opportunity for stillbirth prevention. Indeed, although 25% of



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Figure 3 \*P < .5 for 1961-1969 compared with 1980-1988 rates. Reprinted from Fretts RC, Boyd ME, Usher RH, Usher HA. The changing pattern of fetal death 1961-1986. *Obstet Gynecol* 1992;79:37.

stillbirths that occurred in women carrying a SGA fetus had known risk factors such as maternal hypertension, most pregnancies that ended in stillbirth in nonanomalous growth-restricted fetuses had not been identified as having a problem with fetal growth.

Between 24 and 27 weeks of gestation, the most common causes of stillbirth were related to infection (19%), abruption (14%), or significant lethal anomalies (14%), and 21% were “unexplained.” As noted previously, stillbirths related to infection occur most frequently in fetuses weighing less than 1000 g. The stillbirth rates due to infection, like that of preterm birth, have been quite resistant to change despite the availability and wide use of antibiotics.<sup>10</sup> The risk of a fetal death due to abruption has actually decreased modestly over several decades, although it also remains a significant cause of perinatal morbidity and mortality.

**Unexplained stillbirth**

After 28 weeks of gestation, the most common category of a stillbirth is that of “unexplained,” followed by

deaths related to fetal malnutrition, and abruption (Table I.) The proportion of fetal deaths that have no known cause after complete pathologic evaluation increases as gestational age advances.<sup>10</sup> A fetal death that is unexplained by fetal, placental, maternal, or obstetric factors is the most frequent type of fetal demise, representing between 25% and 60% of all fetal deaths.<sup>13-17</sup> It is also one of obstetrics’ most distressing outcomes, because preventative effective strategies have not yet been identified, in large part because unexplained fetal demise is, by definition, a diagnosis of exclusion and depends on the rigorosity of the stillbirth assessment.<sup>15</sup>

In the first comprehensive analysis of a single large database, Yudkin et al<sup>13</sup> evaluated the timing of fetal demise in 40,635 deliveries in Oxford, England, from 1978 to 1985, in all gestations of 28 weeks or greater. In their examination of 63 unexplained fetal deaths (ie, 43% of all fetal deaths) in this cohort, they found that the risk of unexplained fetal demise more than doubled in pregnancies of greater than 40 weeks of gestation. In the largest study of unexplained stillbirth to date, Huang

**Table I** Most frequent types of stillbirth according to gestational age

24-27 weeks	28-36 weeks	37+ weeks
Infection (19%)	Unexplained (26%)	Unexplained (40%)
Abruptio placenta (14%)	Fetal malnutrition (19%)	Fetal malnutrition (14%)
Anomalies (14%)	Abruptio placenta (18%)	Abruptio placenta (12%)

Fetal malnutrition was defined as an otherwise unexplained fetus weighing less than the 2.4%, anomalies were only considered a cause of death if they were potentially lethal. The unexplained stillbirth was diagnosed when other causes of death were eliminated with the use of a comprehensive evaluation that included autopsy in 97% of cases. Adapted from Fretts et al<sup>10</sup> and Fretts and Usher.<sup>20</sup>

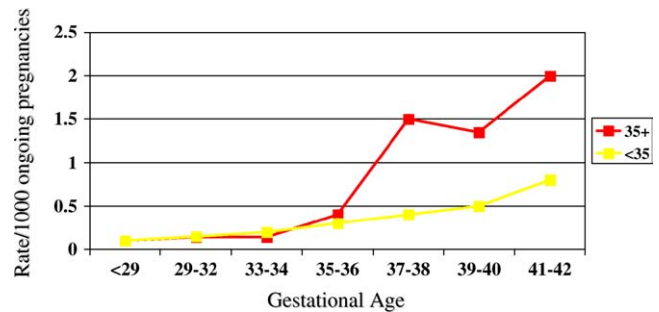
et al<sup>14</sup> described a number of apparent risk factors for unexplained stillbirth in a cohort of women from 1978 to 1996. These risk factors included advanced maternal age (ie, 40 years or older, OR = 3.7, 95% CI 1.3-10.6), low educational attainment (OR = 2.5, 95% CI 1.1-5.5), alterations in fetal growth (ie, between the 2.4-10.0 percentile OR = 2.8, 95% CI 1.5-5.2), infants larger than the 87th percentile (OR = 2.4, 95% CI 1.3-4.4), primiparity (OR = 1.9, 95% CI 1.1-3.1), parity 3 or greater (OR = 2.4, 95% CI 1.0-5.7), and the presence of cord loops (OR = 1.7, 95% CI 1.0-2.97).

Froen et al,<sup>15</sup> using a large data set from Norway, reported findings similar to those of Huang et al,<sup>14</sup> although with slightly higher risk estimates for advanced maternal age (ie, 35 years or older, OR = 5.1, 95% CI 1.3-19.7), low educational attainment (OR = 3.7, 95% CI 1.5-9.8), prepregnancy obesity, and a body mass index (BMI) of greater than 25 (OR = 2.4, 95% CI 1.1-5.3). Smoking is also associated with the unexplained growth-restricted stillbirth,<sup>18,19</sup> but appeared not to be associated with stillbirths among appropriate-for-gestational age fetuses.<sup>14</sup> With respect to the timing of unexplained fetal deaths, these studies and others have consistently shown increased losses late in pregnancy, with the rate rising significantly after 37 to 39 weeks of gestation.<sup>13-15</sup> In addition, Fretts and Usher,<sup>10</sup> using the McGill Obstetrical Neonatal Database, found that this increase was more pronounced in older women (Figure 4).<sup>20</sup>

## Common risk factors for stillbirth

### Race and socioeconomic factors

Nationally, black women consistently have had approximately twice the risk of stillbirth of white women, although typically these rates are not adjusted for differences in obstetric and socioeconomic factors. In Massachusetts in 2002, for example, the household income for black families was significantly lower than



**Figure 4** Reprinted with permission. Fretts RC, Usher RH. Fetal death in women in the older reproductive age group. *Contemporary Reviews in Obstetrics and Gynecology* 1997;9:173-9.

that of white families, and black women are less likely to receive adequate prenatal care, less likely to have completed a high school education, and more likely to have received publicly funded prenatal care.<sup>21</sup> Black mothers who have had a stillbirth were also less likely than white mothers to have sought obstetric care in the first 3 months of pregnancy.<sup>22</sup>

Even when evaluating only women who had received adequate prenatal care, Vintzileos et al<sup>7</sup> found that, in the United States, black women still had twice the risk of stillbirth when compared with white women. The excess of stillbirth was attributed to higher rates of diabetes, hypertension, placental abruption, and premature rupture of membranes.<sup>7</sup> Given that black women are a relatively high-risk group for stillbirth, increasing access to prenatal care, and the identification and management of those medical and socioeconomic risk factors that contribute to stillbirth obviously will be important.

### Advanced maternal age

Advanced maternal age remains an independent risk factor for stillbirth, even after accounting for medical conditions that are more likely to occur in older women, such as multiple gestation, hypertension, diabetes, previous abortion, and abruptio placenta, all of which are associated with higher rates of stillbirth. Older women are also more likely to have preterm births, and growth-restricted infants.<sup>26-29</sup> Historically, women 35 years or older also have had an increased risk of stillbirth related anomalies.<sup>20</sup> Nevertheless, with the introduction of prenatal diagnostic testing and the availability of elective abortion, where these services are available, there has been a significant reduction in this cause of perinatal demise.<sup>30</sup> Indeed, longitudinal databases that track anomalies show a transfer of fetal deaths from after 20 weeks to elective terminations before 20 weeks.<sup>31</sup> After the introduction of routine prenatal diagnosis in the McGill population, for example, women 35 years or older had fewer stillbirths related to lethal anomalies, declining to that observed in younger counterparts. In recent years in this population, the only type of stillbirth

that was statistically more common in older women was the “unexplained” category of fetal demise, and these were likely to occur late in pregnancy.<sup>20</sup>

## Obesity

The prevalence of maternal obesity is increasing steadily and is associated with an increased risk of fetal macrosomia and perinatal mortality.<sup>32-36</sup> The reasons for this association are speculated to be due to behavioral, socioeconomic, as well as obstetric factors. Obese women are more likely to smoke and to have pregnancies complicated by gestational diabetes and preeclampsia.<sup>37</sup> However, even when controlling for these factors, an elevated BMI remains a significant risk factor for stillbirth,<sup>33,36</sup> and the association appears to increase as the gestation advances. A number of mechanisms for the increased risk seen in obese women have been postulated. Thinner women may be better able to perceive decreased fetal movements. Maternal obesity is also associated with hyperlipidemia,<sup>38</sup> which may contribute to increased endothelial dysfunction, platelet aggregation, as well as to clinically significant atherosclerosis. Sleep studies of pregnant women have shown that obese women spend more time snoring (32% vs 1%;  $P < .001$ ), have more apnea-hypoxia events (1.7 vs 0.2/h;  $P < .05$ ), and have more episodes of oxygen desaturation (5.3 vs 0.3/h;  $P < .005$ ) than nonobese pregnant women.<sup>39</sup> Snoring has also been associated with pregnancy-induced hypertension and fetal growth restriction.<sup>40</sup> Indeed, in addition to advanced maternal age and low socioeconomic status, as discussed previously, the most prevalent risk factor for stillbirth is prepregnancy obesity.

## Thrombophilias

Our understanding of the relationship between inherited abnormalities of blood clotting and stillbirth is seriously deficient, in that there have been no large population-based studies that have evaluated this association.<sup>41-44</sup> The relationship between late fetal death and thrombophilia is more consistent than with early fetal losses,<sup>45</sup> although the odds ratio ranges from as low as 1.8 to estimates as high as 12.<sup>46,47-50</sup> A meta-analysis of smaller studies suggested that the presence of thrombophilias does increase the risk of stillbirth (OR = 3.6; 95% CI 1.4-9.4), with the analysis of specific defects limited by power.<sup>41</sup> Martinelli et al<sup>51</sup> found the prevalence of mutations either in factor V or prothrombin to be 16% in those pregnancies that ended in an unexplained loss, compared with 6% of normal pregnancies,<sup>51</sup> although the value of placental disease to discriminate unexplained losses with and without a diagnosis of thrombophilia is in question. The authors found that 24% of the placentas were normal, whereas the remaining 76% showed intravascular thrombi, decidual vasculopathy, and ischemic necrosis with villous infarctions.

The placentas were abnormal in 7 of 9 (78%) women with a mutation and in 40 of 53 (75%) stillbirths without a mutation so that the presence of a known mutation did not correlate with a specific placental histologic or biochemical abnormality. In another small study of 22 women with at least 1 unexplained loss, 4 of 9 placentas showed extensive infarcts in women who had documented thrombophilia, whereas none of the 8 without thrombophilia exhibited similar pathologic findings.<sup>47</sup>

## Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) complicates less than 1% of pregnancies but the risk of stillbirth in this population is disproportionately high, especially in women with preexisting renal disease.<sup>52</sup> Hypertension, preeclampsia, and fetal growth restriction are common in these patients.<sup>53-55</sup> Even when pregnancy is conceived during a relatively quiescent period in terms of disease activity, stillbirth can complicate up to 3% to 8% of pregnancies.<sup>53-55</sup> The presence of a lupus anticoagulant has been reported to significantly increase the risk of a fetal loss after 20 weeks of gestation. The optimum management of patients with SLE is uncertain, but the use of heparin and aspirin was associated with an improved outcome in 1 small series.<sup>45</sup>

## Medical risk factors

Hypertension and diabetes are 2 of the most common medical conditions to complicate pregnancy (7%-10% and 3%-5%, respectively).<sup>23,52,56-59</sup> Historically, both of these conditions have been shown to be responsible for a significant proportion of fetal deaths. However, optimal management, including counseling, preconceptional care, and close medical management of these conditions, has been shown to reduce the risk for perinatal death to a level only marginally elevated over that of the general population.<sup>56</sup> Management of patients remains a challenge, however, because of the increased risks of abruptio placenta, of intrauterine growth restriction, and of superimposed preeclampsia, which often necessitates early delivery.<sup>57,58,60</sup> Other important medical conditions associated with an increased risk of stillbirth are listed in Table II.<sup>52</sup>

## Infection and immunologic exposure

A significant proportion of perinatal morbidity and mortality is related to infection, which often leads to delivery of a premature liveborn or a stillborn infant. Despite the adoption of a strategy to reduce the risk of perinatal infection caused by group B streptococci, there has been little change in the risk of fetal death caused by infection because most of these deaths occur preterm.<sup>10,61</sup> Although there are some pathogens that are probable causes of stillbirth, such as parvovirus 19,

**Table II** Estimates of maternal risk factors and risk of stillbirth

Condition	Prevalence	Estimated rate of stillbirth	OR*
All pregnancies		6.4/1000	1.0
Low-risk pregnancies	80%	4.0-5.5/1000	0.86
Hypertensive disorder			
Chronic hypertension	6%-10%	6-25/1000	1.5-2.7
Pregnancy-induced hypertension			
Mild	5.8%-7.7%	9-51/1000	1.2-4.0
Severe	1.3%-3.3%	12-29/1000	1.8-4.4
Diabetes			
Treated with diet	2.5%-5%	6-10/1000	1.2-2.2
Treated with insulin	2.4%	6-35/1000	1.7-7.0
SLE	< 1%	40-150/1000	6-20
Renal disease	< 1%	15-200/1000	2.2-30
Thyroid disorders	0.2%-2%	12-20/1000	2.2-3.0
Thrombophilia	1%-5%	18-40/1000	2.8-5.0
Cholestasis of pregnancy	< 0.1%	12-30/1000	1.8-4.4
Smoking > 10 cigarettes	10%-20%	10-15/1000	1.7-3.0
Obesity (prepregnancy)			
BMI 25-29.9 kg/m <sup>2</sup>	21%	12-15/1000	1.9-2.7
BMI > 30	20%	13-18/1000	2.1-2.8
Low educational attainment (< 12 y vs. 12 y+)	30%	10-13/1000	1.6-2.0
Previous growth-restricted infant (< 10%)	6.7%	12-30/1000	2-4.6
Previous stillbirth	0.5%-1.0%	9-20/1000	1.4-3.2
Multiple gestation	2%-3.5%		
Twins	2.7%	12/1000	1.0-2.8
Triplets	0.14%	34/1000	2.8-3.7
Advanced maternal age (reference < 35 y)			
35-39 y	15%-18%	11-14/1000	1.8-2.2
40y +	2%	11-21/1000	1.8-3.3
Black women compared with white women	15%	12-14/1000	2.0-2.2

\* OR of the factor present compared to the risk factor absent. Some estimates of medical conditions and stillbirth risk from Simpson.<sup>52</sup> Other risk estimates from references 24,25,29,33,34,35,38,55,58,68.

cytomegalovirus, toxoplasmosis, and listeria, there are others that may be associated with an increase in risk, but the evidence for which remains inconclusive. For example, colonization with *Ureaplasma urealyticum*, *Mycoplasma hominis*, and group B streptococci has all been associated with an increased risk of stillbirth,<sup>61</sup> although colonization with these pathogens is also common among healthy women.

In recent reports, Refuerzo et al<sup>62</sup> and Blackwell et al<sup>63</sup> found that women who had had an unexplained stillbirth, without any evidence of obvious infection, had a higher number of “memory T cells” (CD45RO) than “naive T cells” (CD45RA) when compared with live-born controls. Although this finding suggests that, despite the absence of any overt evidence of clinically significant infection, these women had had prior exposure to infectious agents. Froen et al<sup>64</sup> found, in an epidemiologic study of unexplained stillbirths, that bacteruria or symptomatic urinary tract infections during pregnancy were associated with a *reduced* risk of fetal death, a finding not fully explained by treatment with antibiotics. The role of the immune system has lately become a subject of considerable interest in

perinatal birth injury. There is evidence that elevated inflammatory processes are associated with an increase in the risk of adverse outcomes in the premature neonate.<sup>65</sup> Infected infants, both premature and term, were shown to exhibit a significant increase in interleukin 6 production, with C-reactive protein (CRP) increasing rapidly at the onset of infection and remaining elevated until the infection was cleared.<sup>66</sup> Animal data suggest that the combination of subclinical infection and a fetal inflammatory response can both cause abnormalities of gas exchange that result in fetal hypoxia and decreased survival.<sup>67</sup>

## Infertility

Because women who choose to delay their childbearing are also more likely to have a history of infertility and to conceive with the aid of reproductive technologies, it is important to evaluate the effect of infertility and infertility treatment on the risk of fetal death. Patients treated with advanced reproductive technologies experience excess perinatal mortality.<sup>68-70</sup> Although the frequency of multiple gestations is responsible for a

significant portion of this excess mortality, it also appears that women who undergo either in vitro fertilization (IVF) or ovarian stimulation and have a singleton gestation, also have a statistically increased risk of prematurity, low birth weight, and SGA fetuses.<sup>71-74</sup> There have been no studies that have evaluated whether infertility itself is associated with an increase in unexplained fetal death. Nevertheless, many physicians who care for infertile patients perceive these pregnancies to be at “high risk” for adverse maternal and fetal outcomes.

## Multiple gestations

Over the past 2 decades, the rate of pregnancies with twins has more than doubled, the rate of triplets has increased 6-fold, and the number of quadruplets has increased by 12-fold.<sup>68-70</sup> With this increase in the number of multiple gestations, there has been a measurable increase in prenatal mortality and morbidity in industrialized countries. The main reason for this increase is the use of reproductive technologies and the associated increase in maternal age.<sup>75,76</sup> It has been estimated that a strategy of lowering the transfer rate to 2 embryos during IVF could reduce the perinatal mortality rate by 45% in the case of limiting a triplet to twins, or 74% when limiting the quintuplet pregnancies to twins.<sup>70</sup> The optimal duration of an otherwise uncomplicated pregnancy is shorter for multiple gestations. Kahn et al<sup>77</sup> found, for example, that it was safer for a twin pregnancy to be delivered than undelivered at 39 weeks, and for triplets who remain undelivered at 36 weeks, an elective delivery at this time minimized adverse fetal outcomes.

## Biologic markers of increased risk of stillbirth

### Hemoconcentration

Froen et al<sup>64</sup> from Norway have demonstrated that women with hemoconcentration, defined as the lowest hemoglobin measured during pregnancy greater than 13.0 g/dL, is associated with a 9-fold increase in the risk of unexplained fetal death. Stephansson et al,<sup>78</sup> using a Swedish database, found that both an initial elevated hemoglobin and the failure of significant hemodilution over the course of the pregnancy, increased the risk of stillbirth by 2-fold, even when women with preeclampsia and eclampsia were excluded.<sup>78</sup> Plasma volume expansion and lowered hemoglobin concentration are normal physiologic responses to pregnancy. Plasma volume expansion appears to be important for fetal growth and failure of sufficient hemodilution is associated with an increased risk of stillbirth, even if the fetus is not growth restricted. Stephansson et al<sup>78</sup> suggest that those

patients with high initial hemoglobin concentrations should be considered at high risk for adverse obstetric outcomes.

### Amniotic and serum markers

Pregnancy-associated plasma protein A (PAPP-A) is a maternal serum marker used in combination with other tests to detect an increased risk of chromosomal abnormalities; it also appears to be of help in detecting, in the second trimester, pregnancies that might be at an increased risk for an adverse outcome. Smith et al<sup>79</sup> assessed adverse perinatal outcomes among the 8839 patients recruited into a multicenter study. Patients with serum markers in the lowest fifth percentile were found to have an increased risk of premature delivery (OR = 2.9, 95% CI 1.6-5.5), preeclampsia (OR = 2.3, 95% CI 1.6-3.3), and stillbirth (OR = 3.6, 95% CI 1.2-11.0).<sup>79</sup> In growth-restricted fetuses, the maternal serum alpha-fetoprotein was not particularly helpful in identifying pregnancies that would later go on to an adverse perinatal outcome, but a combination of factors, an elevated HCG and a low unconjugated estriol, was 67% sensitive and 70% specific in predicting a composite “adverse perinatal outcome” metric, which included perinatal death and neonatal morbidity.<sup>80</sup>

Amniotic fluid abnormalities also have been found to be associated with fetal demise. Florio et al<sup>81</sup> performed a case control study of women undergoing amniocentesis for routine reasons, in which 12 patients with a stillbirth all had elevated levels of S100B (a marker of brain damage in both adult and pediatric patients, but which is not specific for cerebral damage),<sup>82</sup> but the 746 healthy controls did not. At least in this dataset, this test was perfect in predicting fetal death, a very rare finding in medicine, although these data will need to be replicated.<sup>81</sup> The mechanisms linking most abnormal maternal serum and amniotic markers with adverse fetal outcomes are not known, but further study is required before recommendations for specific clinical applications can be considered.

## Prevention strategies

The data available for cost-effective stillbirth prevention are limited. The remaining aspect of this review represents the author’s opinion based on the limited data available. In the absence of a prior obstetric history, the patient’s risk for stillbirth is related to her underlying health and lifestyle. Globally, one of the largest modifiable risk factors is smoking, as it is obviously tied to the pathophysiology of many diseases. Additional medical risk factors, as discussed previously, significantly impact both maternal and child health as well, and appropriate medical care for these conditions and preconception counseling can have a significant impact

on outcome. The provider should perform a risk assessment for each individual patient and give realistic estimates of anticipated obstetric outcomes. Screening for hypertension and diabetes are essential to prevent poor pregnancy outcomes, but a number of other factors should be included in any risk assessment, including advanced maternal age, prepregnancy obesity, infertility, low educational attainment as a marker of lower socioeconomic status, and black race.<sup>7,8,25,33</sup> Although the black race may be a proxy for socioeconomic factors, it is helpful to remember that black women 35 years or older have a risk of stillbirth 4 to 5 times higher than the national average and therefore deserve the same vigilance afforded to other groups at high risk for stillbirth.<sup>6</sup>

A moderate proportion of stillbirths related to congenital anomalies could be reduced with preconceptual counseling and testing, adequate prenatal care, and prenatal diagnostic testing, with elective terminations for affected pregnancies.<sup>30</sup> During pregnancy, patients with medical conditions need to be closely monitored to optimize their treatment and fitness for pregnancy and ensure fetal well-being.

In terms of reducing potentially preventable stillbirths, the Confidential Inquiry into Stillbirths and Infant Death (CISID) of Northern Ireland found that the failure to adequately diagnose and manage fetal growth restriction was the most common error, followed by failure to recognize additional maternal medical risk factors.<sup>83</sup> Given that deaths of intrauterine growth-restricted fetuses represent 1 of the most common types of stillbirths,<sup>84,85</sup> a significant opportunity remains to improve outcomes. Assessment of fetal growth by ultrasound should be considered in at-risk patients. A customized growth chart more readily identifies the growth-restricted fetus, and reduces "false alarms" in the constitutionally small fetus.<sup>86</sup> Ideally, serial ultrasound reports should be reported together so that the history of intrauterine growth over time can be more readily appreciated. The threshold to perform an ultrasound in the obese patient should be low because fetal growth is often difficult to estimate clinically.

In women who have had a previous pregnancy, a previous preterm delivery, previous obstetric complication, delivery of a growth-restricted fetus, or a stillborn fetus, these events significantly increase their risk for adverse events in future pregnancies.<sup>87-89</sup> There is some evidence, for example, that a previous cesarean section at term might reduce placental function and therefore increase the risk of a late antepartum unexplained stillbirth.<sup>90</sup> Nevertheless, this association should be confirmed by other groups before it is considered an important risk factor.

Given all of the potential factors that influence the risk of stillbirth, it would be helpful to have an interactive model that would estimate the risk of a fetal

demise in a manner similar to that used by physicians who care for patients with cardiovascular risk factors, who have a wealth of information to estimate the risk of myocardial infarction and death. A risk analysis should guide management policies and provide an evidenced-based approach to alter the threshold at which antepartum testing and early delivery is considered. Until such evidence-based guidelines exist, the obstetric care provider must decide on the appropriate type of vigilance, and decide when expectant care increases the risk to the ongoing pregnancy to a degree that warrants intervention for delivery.<sup>91,92</sup>

Fortunately, for the majority of obstetric patients who are low risk, the incidence of a late stillbirth is a relatively low (1-2/1000).<sup>93</sup> Still, there is a role for vigilance in these pregnancies. In a reanalysis of the results of a fetal movement counting study initially published by Grant et al,<sup>94</sup> Froen<sup>95</sup> has appropriately reignited the interest in fetal kick counting. Even low-risk pregnancies with decreased fetal movement are known to have a higher risk of fetal distress in labor, for being growth restricted, and for having an increased frequency of stillbirth.

The risk of stillbirth in late pregnancies has been appreciated by many authors, as discussed previously.<sup>96-101</sup> Antepartum surveillance with judicious delivery of fetuses with poor fetal testing has been shown to improve outcomes in pregnancies with growth-restricted fetuses.<sup>102</sup> Antepartum testing is also widely used in patients perceived to be at increased risk for fetal death, with the use of the testing related to the underlying risk of stillbirth.<sup>102</sup> Randomized control trials of expectant versus induction of the postdates pregnancy are not large enough to detect a difference in the perinatal mortality.<sup>103</sup> However, in an analysis of the effect of labor induction rates in the 41st week, Sue et al<sup>104</sup> found that in Canada between 1980 and 1995 there was a marked decrease in the number of pregnancies at 41 or more weeks of gestation. The authors correlated the increase in the number of inductions after 41 weeks to a lowering of the stillbirth rate.<sup>104</sup> Fretts et al,<sup>93</sup> using the McGill Obstetrical Neonatal Database to obtain risk estimates, performed a decision-analysis of the risks and benefits of antepartum testing late in pregnancy for women 35 years or older. This decision analysis considered only late unexplained stillbirth, but this covers the majority of late stillbirths.<sup>93</sup> For the neonate, there is no measurable long-term adverse effect of being born at 36 weeks of gestation or later, so the analysis was begun starting during the 37th week. The major risk of antepartum testing after 36 weeks is induction of labor and its associated downstream effects, such as a potential for an increase in the cesarean delivery rate,<sup>105</sup> and therefore a potential increase the maternal mortality rate. For multiparous patients, induction carries a lower risk, and although induction does probably increase the risk of cesarean delivery, it does so only

**Table III** Unexplained stillbirth risks and outcomes of weekly antepartum testing initiated at the 37th week of gestation

Outcome*	OR for unexplained stillbirth				
	1.0	2.0	3.0	4.0	5.0
Fetal deaths per 1000 with antepartum testing	0.4	0.8	1.2	1.5	1.9
Fetal deaths averted <sup>†</sup>	1.2	2.4	3.5	4.7	5.9
Tests per pregnancy	3.4	3.4	3.3	3.3	3.3
Tests per fetal death averted	2862	1418	950	711	569
Inductions per fetal death averted	233	116	78	58	47
Cesarean deliveries per fetal death averted	44	22	15	11	9

Assuming base-case test characteristics (70% sensitivity, 90% specificity).

\* Outcomes from week 37 of gestation through week 41.

<sup>†</sup> Unexplained fetal deaths averted per 1000 pregnancies compared to no testing.<sup>93</sup>

marginally.<sup>106</sup> In the initial study by Fretts et al<sup>93</sup> on the risks and benefits of antepartum testing late in pregnancy for older women, they constructed a sensitivity analysis that applies to any condition associated with an increased risk of late stillbirth.<sup>93</sup> Three strategies were compared: no testing, testing after the 36th week with induction for a positive test, and no testing with induction at 41 weeks. The number of fetal deaths averted and the number of tests, inductions, and additional cesarean deliveries per fetal death averted were calculated assuming antepartum testing to be 70% sensitive and 90% specific. The results for OR 1.0 to 5.0 are presented in Table III.

Although a strategy of antepartum testing is predicted to be most successful in reducing the number of unexplained stillbirths, it was also associated with the highest induction rate. For nulliparous women of advanced maternal age, predicted to have an OR of 3.3 over younger women, the number of additional cesarean deliveries performed for unsuccessful inductions was only 14 per fetal death averted. The model also estimated that it would take approximately 863 antepartum tests and 71 additional inductions to prevent 1 unexplained stillbirth. Nevertheless, a strategy of liberal antepartum testing, to identify at-risk pregnancies will also reduce the number of patients undelivered at each gestational age starting at the time that testing is initiated, thereby further reducing the number of pregnancies still at risk of a stillbirth.

## Management of stillbirth

The diagnosis of a singleton stillbirth must be confirmed with an ultrasound examination of the fetal heart. Most hospitals have instituted a program to help bereaved parents cope with their loss and follow good practice guidelines, which include the opportunity to see and hold their infant and obtain tokens of remembrance.<sup>107</sup> A worksheet for both parents and providers help to streamline the management of these losses and can facilitate the optimal investigation for determining the cause of death. Delayed delivery after 24 hours of the

diagnosis has been associated with an increased risk of anxiety years after the loss, when compared with women whose labors were induced within 6 hours.<sup>108</sup> The expectant management of a stillbirth therefore should be discouraged, in addition to the fact that delayed delivery is also associated with increased maternal risks of consumptive coagulopathy.<sup>109,110</sup> The availability of prostaglandins, in particular misoprostol, has made induction of stillbirth safer and more efficient in women without a previous cesarean delivery. For now, oxytocin will remain the main method of induction for women with a previous cesarean delivery.

After delivery, the parents and other family members should have the opportunity to spend as much time as needed with the deceased infant. Even in the scenario of obvious maceration of the infant, after initial anxiety, parents often find something to connect them to the infant. A recent study has questioned whether holding a stillborn child might increase the risk of later anxiety,<sup>111</sup> this finding has not been duplicated to date.

One important aspect of a woman's care after a stillbirth is an appropriate and comprehensive stillbirth assessment. It is unfortunate that the United States has 1 of the lowest rates of obtaining a comprehensive stillbirth assessment when compared with other developed countries. This may be in part due to an increased level of anxiety over litigation in the United States, but it may also reflect the absence of a nationally coordinated program to evaluate these deaths. Notwithstanding, there are centers within the United States that can serve as role models for a comprehensive approach to stillbirth such those at the University of Southern California and the Wisconsin Stillbirth Service Program.<sup>112,113</sup> Incerpi et al<sup>113,114</sup> have demonstrated that, within the context of developing a cost-effective stillbirth assessment program, the single most important test to determine the cause of a stillbirth is the autopsy, followed by an evaluation of the placenta. For some parents, a limited fetal evaluation will be more acceptable than a complete autopsy, and this option should be explored if a complete autopsy is not acceptable.<sup>115,116</sup> An external

physical examination and radiologic testing performed by the perinatal pathologist, with or without sampling fetal tissues in situ, can provide significant information. Although an autopsy is optimal, a postmortem magnetic resonance image (MRI) can provide useful additional information, although typically MRI staff are not used to receiving these requests.<sup>117</sup>

A genetic analysis of chromosomes will reveal abnormalities in between 5% and 10% of stillbirths.<sup>113</sup> After a stillbirth, the highest yield for obtaining fluid for cytogenetic analysis will be at the time of amniocentesis at the time of the diagnosis of the stillbirth, but this has not been the usual practice at most centers of care within the United States. If amniotic fluid is unavailable, a sample of fetal blood, skin, or fascia lata will be best sources of tissue for culture. The use of a cytogenetic evaluation decreases with the duration of time that the infant has been dead, so reserving placental tissue for fluorescence in situ hybridization (FISH) in a buffered saline solution is an alternative method of determining whether the infant had a common chromosomal abnormality.<sup>118,119</sup>

With the use of a protocol of autopsy, evaluation of the cord/placenta and membranes, and laboratory tests of fasting glucose, a Kleihauer-Betke test, urine toxicology and hemoglobin A<sub>1c</sub> in selected cases, and a thrombophilia workup in normally formed infants, Incerpi et al<sup>113</sup> were able to attribute a primary cause of death in 72% of cases of stillbirth, leaving only 28% as "unexplained." Notably absent in their protocol was the recommendation of obtaining TORCH titers, (ie, cytomegalovirus, toxoplasmosis, herpes simplex virus, and rubella) because these titers, in and of themselves, almost never aid in the diagnosis of a congenital infection in the absence of autopsy and placental findings of infection. Incerpi et al<sup>120</sup> found no significant association between antinuclear antibodies and stillbirth in the evaluation of 286 unexplained stillbirths. Parvovirus 19 is most commonly associated with a fetal death in the setting of nonimmune hydrops, but parvovirus 19 DNA can also be found in the placenta and fetus even in the nonhydropic infant.<sup>121,122</sup>

The value of a comprehensive stillbirth assessment cannot be underestimated, because the results are relevant to assess the risk of recurrence, the development of prenatal diagnostic recommendations for subsequent pregnancies. Pauli's group at the Wisconsin Stillbirth Service, a model state-wide program for the prevention of stillbirth, estimated that in 2001, the real cost of a stillbirth assessment was approximately \$1450 US or approximately \$12 per cared-for pregnancy, and influenced subsequent perinatal care in 51% of cases.<sup>112</sup> After studying 1631 stillbirths, the most significant consequence of this analysis was the change in the risk estimate of recurrence or stillbirth in 42% of cases. Other consequences were a change in the recommenda-

tions with respect to prenatal diagnosis in 22.2% and preconceptional management in 10.9% of subsequent pregnancies.

## Summary

Clinicians need to be able to assess each patient's risk for adverse outcomes, including stillbirth, and to have a low threshold to evaluate fetal growth in at-risk pregnancies. As reviewed previously, late pregnancy is also associated with progressively increasing risk of stillbirth, and although the strategy of antepartum testing in patients with increased risk will decrease the risk of late fetal loss, it is of necessity also associated with higher intervention rates.

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