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Management of Stillbirth

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ABSTRACT: Stillbirth is one of the most common adverse pregnancy outcomes, occurring in 1 in 160 deliveries in the United States. In developed countries, the most prevalent risk factors associated with stillbirth are non-Hispanic black race, nulliparity, advanced maternal age, obesity, preexisting diabetes, chronic hypertension, smoking, alcohol use, having a pregnancy using assisted reproductive technology, multiple gestation, male fetal sex, unmarried status, and past obstetric history. Although some of these factors may be modifiable (such as smoking), many are not. The study of specific causes of stillbirth has been hampered by the lack of uniform protocols to evaluate and classify stillbirths and by decreasing autopsy rates. In any specific case, it may be difficult to assign a definite cause to a stillbirth. A significant proportion of stillbirths remains unexplained even after a thorough evaluation. Evaluation of a stillbirth should include fetal autopsy; gross and histologic examination of the placenta, umbilical cord, and membranes; and genetic evaluation. The method and timing of delivery after a stillbirth depend on the gestational age at which the death occurred, maternal obstetric history (eg, previous hysterotomy), and maternal preference. Health care providers should weigh the risks and benefits of each strategy in a given clinical scenario and consider available institutional expertise. Patient support should include emotional support and clear communication of test results. Referral to a bereavement counselor, peer support group, or mental health professional may be advisable for management of grief and depression.

Purpose

Stillbirth is one of the most common adverse pregnancy outcomes, occurring in 1 in 160 deliveries in the United States. Approximately 23,600 stillbirths at 20 weeks or greater of gestation are reported annually (1). The purpose of this document is to review the current information on stillbirth, including definitions and management, the evaluation of a stillbirth, and strategies for prevention.

Background

Definition

The U.S. National Center for Health Statistics defines *fetal death* as the delivery of a fetus showing no signs of life as indicated by the absence of breathing, heartbeats, pulsation of the umbilical cord, or definite movements of voluntary muscles (1). There is not complete uniformity among states with regard to birth weight and gestational age criteria for reporting fetal deaths. However, the suggested requirement is to report fetal deaths at 20 weeks or greater of gestation (if the gestational age is known), or a weight greater than or equal to 350 grams if the gestational age is not known (2). The cutoff of 350 grams is the 50th percentile for weight at 20 weeks of gestation.

To promote the comparability of national data by year and state, U.S. vital statistics data are collected for fetal deaths with a stated or presumed period of gestation of 20 weeks or more (1). Terminations of pregnancy for life-limiting fetal anomalies and inductions of labor for previable premature rupture of membranes

are specifically excluded from the stillbirth statistics and are classified as terminations of pregnancy (1).

The term stillbirth is preferred among parent groups, and more recent research efforts have begun using this term in place of fetal death. Therefore, in this document, the term stillbirth is used.

Frequency of Occurrence

In 2013, the stillbirth rate in the United States was 5.96 per 1,000 live births, a decrease from 6.61 in 2006 and 6.05 per 1,000 births in 2012 (1). Between 2006 and 2012, the rate of early stillbirth (20–27 weeks) remained essentially unchanged, but between 2012 and 2013, the rate decreased from 3.11 to 3.01 per 1,000 births. The rate of late stillbirth (28 weeks or greater) has been relatively stable since 2006 and did not change significantly between 2012 and 2013 at 2.96 and 2.97 per 1,000 births, respectively (1). There is ongoing discussion regarding the most useful calculation for analysis of stillbirth occurrences. Currently, fetal mortality rates are widely calculated using a birth-based approach: the number of stillbirths per 1,000 live births and stillbirths (1).

There may be some utility in changing the denominator to better capture the population at risk, that is, all women who are still pregnant at a given gestational age. Using a denominator of women who are still pregnant at a given gestational age allows for calculation of a *prospective fetal mortality rate* defined as the number of stillbirths at a given gestational age (in single weeks) per 1,000 live births and stillbirths at that gestational age or greater (3). This approach produces the prospective risk of stillbirth, which can be clinically valuable to make predictions for individual pregnancies and to help health care providers balance the risks of expectant management with those of intervention (1) (Fig. 1).

Risk Factors

In developed countries, the most prevalent risk factors associated with stillbirth are non-Hispanic black race, nulliparity, advanced maternal age, obesity, preexisting diabetes, chronic hypertension, smoking, alcohol use, having a pregnancy using assisted reproductive technology, multiple gestation, male fetal sex, unmarried status, and past obstetric history (4, 5). Although some of these factors may be modifiable (such as smoking), many are not.

Social Demographic Factors Affecting Stillbirth

Race. Non-Hispanic black women have a stillbirth rate that is more than twice the rate of other racial groups (10.53 deaths per 1,000 livebirths and stillbirths) (1). In the United States, the stillbirth rates for other groups were 4.88 for non-Hispanic white women, 5.22 for Hispanic women, 6.22 for American Indian or Alaska Native, and 4.68 for Asian or Pacific Islanders (1).

The reason for this health care disparity in stillbirth rates is multifactorial and the subject of ongoing research (6). Higher rates of stillbirth persist among non-Hispanic black women with adequate prenatal care; this has been attributed to higher rates of diabetes mellitus, hypertension, placental abruption, and premature rupture of membranes (7, 8). The educational level for Hispanic and non-Hispanic black women does not appear to be protective as compared with white women, with the widest disparities observed between white and non-Hispanic

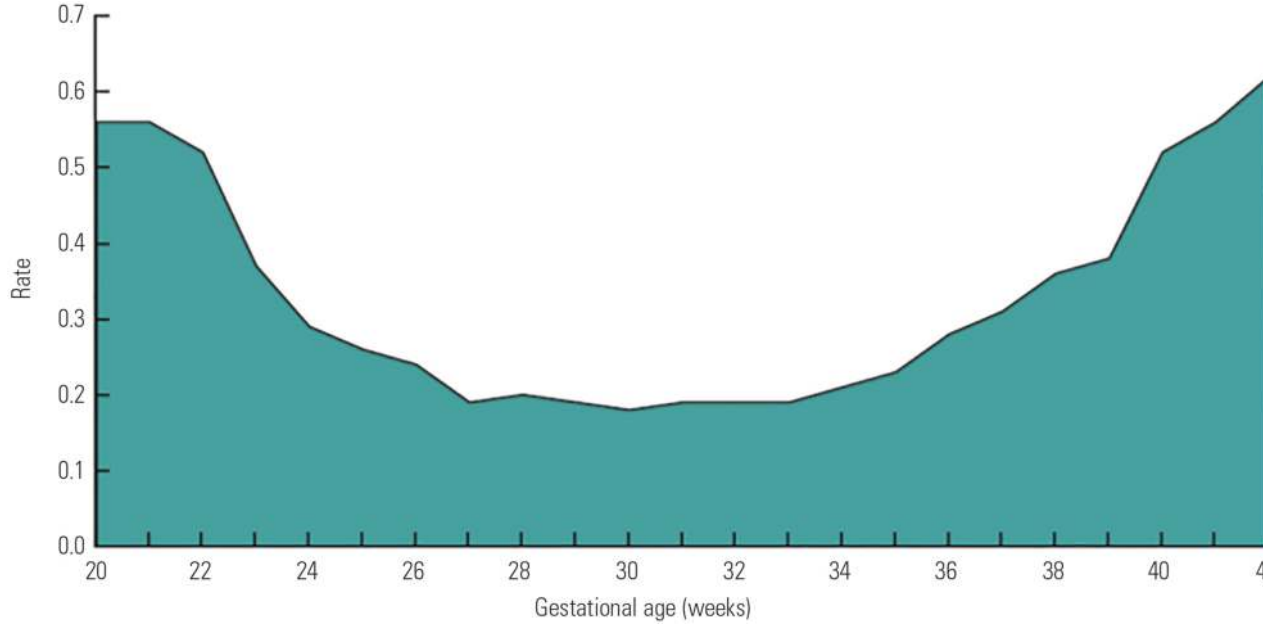

Figure 1. Prospective fetal mortality rate, by single week of gestation: United States, 2013. Note: The prospective fetal mortality rate is the number of stillbirths at a given gestational age per 1,000 live births and stillbirths at that gestational age or greater. (MacDorman MF, Gregory ECW. Fetal and perinatal mortality: United States, 2013. National vital statistics reports; vol. 64 no. 8. Hyattsville, MD: National Center for Health Statistics. 2015.)

black stillbirths at 20–27 weeks of gestation, regardless of educational attainment (9). Implicit and explicit bias and racism are implicated in many health disparities including perinatal morbidity and mortality (10). It remains to be better characterized how biologic and modifiable risk factors, including care disparities and environmental stressors, biases, and racism further contribute to the risk for non-Hispanic black women (11).

Multiple Gestations

The stillbirth rate among twin pregnancies is approximately 2.5 times higher than that of singletons (14.07 versus 5.65 per 1,000 live births and stillbirths) (1). The risk of stillbirth increases in all twins with advancing gestational age, and it is significantly greater in monochorionic as compared with dichorionic twins (12). The stillbirth rate for triplet pregnancies and higher order multiples is reported as 30.53 per 1,000 live births and stillbirths. Higher rates are due to complications specific to multiple gestation (such as twin–twin transfusion syndrome), as well as to increased risks of common complications such as aneuploidy, congenital anomalies, and growth restriction (1, 13).

Past Obstetric History

Women with a previous stillbirth are at increased risk of recurrence. Compared with women with no history of stillbirth, women who had a stillbirth in an index pregnancy had an increased risk in subsequent pregnancies (pooled odds ratio, 4.83; 95% CI, 3.77–6.18), which remained significant after adjustment for confounding factors (14).

Women with previous adverse pregnancy outcomes, such as preterm delivery, growth restriction, or preeclampsia, are at increased risk of stillbirth in subsequent pregnancies (15). The relationship between previous adverse pregnancy outcomes and stillbirth is strongest in the case of explained stillbirth. However, there remains a persistent 1.7-fold to 2-fold increase in unexplained stillbirth associated with a history of adverse pregnancy outcomes. In a study that examined previous preterm and small for gestational age (SGA) births and the risk of stillbirth in a subsequent pregnancy, the risk of stillbirth was increased in the setting of a prior SGA infant; the highest risk was for a prior SGA infant born at less than 32 weeks (OR, 8.0; 95% CI, 4.7–13.7) (16).

The relationship between previous cesarean delivery and subsequent stillbirth remains controversial. In two large studies from the United Kingdom, previous cesarean delivery was associated with an increased rate of explained (17) and unexplained stillbirth (15) with an adjusted hazard ratio ranging from 2.08 (95% CI, 1.00–4.31) and 1.75 (95% CI, 1.30–2.37), respectively, for all causes of subsequent stillbirth. A Danish analysis showed a slight increase in the rate of stillbirth after cesarean in explained and unexplained stillbirths, but neither reached statistical significance (18). In addition, three large observational studies from the United States (19–21) and one from Canada (22) found no association between history of cesarean and stillbirth. In the largest of these studies, the unexplained stillbirth rates at term for women with and without a previous cesarean delivery were 0.8 and 0.7 per 1,000 births, respectively (relative risk [RR] 0.90; 95% CI, 0.76–1.06) (20).

The extremes of parity have also been associated with stillbirth. Higher rates of stillbirth are observed in nulliparous women as well as multiparas women with greater than three previous pregnancies when compared to women with one or two previous births (23).

Male sex

Male sex of the fetus has been observed as a risk factor for stillbirth. In a recent review of data from more than 30 million births, in a wide range of high-income and low-income countries, the crude mean rate (stillbirths per 1,000 total births) was 6.23 for males and 5.74 for females. The pooled RR was 1.10 (95% CI, 1.07–1.13), which indicates that a male fetus has approximately a 10% higher risk for stillbirth (24). Although this meta-analysis identifies fetal sex as an important risk factor for stillbirth, the reason why males are at higher risk is unknown.

Younger and Older Maternal Age

Maternal age at either end of the reproductive age spectrum (less than 15 years and greater than 35 years) is an independent risk factor for stillbirth. Maternal age greater than or equal to 35 years of age is associated with an increased risk of stillbirth in nulliparous and multiparous women (25, 26). A significant proportion of perinatal deaths seen in older women are related to lethal congenital and chromosomal anomalies. The introduction of population-based screening for chromosomal abnormalities has contributed to lower rates of explained stillbirth or neonatal death resulting from chromosomal abnormalities (27). Large observational studies demonstrate that advanced maternal age is an independent risk factor for stillbirth even after controlling for risk factors such as hypertension, diabetes, placenta previa, and multiple gestation (26, 28, 29). In addition, there appears to be an interaction between first birth and increasing maternal age that places nulliparous older women at higher risk (27). Based on one study, the estimated risk of stillbirth is 1 in 116 in a 40-year-old nulliparous woman after 37 weeks of gestation, compared with 1 in 304 in a multiparous woman of the same age (27).

The stillbirth rate for teenagers younger than 15 years of age is 15.88 per 1,000 live births. This is nearly three times the rate of the lowest risk group, aged 25–29 years, with a rate of 5.34 per 1,000 live births. The rate for teenagers aged 15–17 years was 7.03 per 1,000, and the rate for 18–19-year olds was 6.52 per 1,000 live births. These were 32% and 22% higher than the lowest risk age group (1). This bimodal peak at extremes of reproductive age has been observed in several studies as well as confirmed in a large population-based cohort study using the Centers for Disease Control and Prevention's "Linked Birth-Infant Death" and "Fetal Death" data files of 37,504,230 births (30).

Comorbid Medical Conditions

Many maternal medical conditions are associated with an increased risk of stillbirth (Table 1). Hypertension and diabetes are two of the most common comorbid pregnancy conditions (4, 31). Population-based studies demonstrated almost a twofold to fivefold increase in the risk of stillbirth among women with pregestational diabetes and gestational diabetes (4, 32–34). There appears to be a joint effect of pregestational diabetes and obesity that is stronger than the individual effects of each risk factor (35). However, with prepregnancy strict glycemic control aiming for $HgbA_{1C}$ values less than 7% and maintenance of maternal euglycemia during pregnancy, the risk of stillbirth may be reduced (36, 37). The perinatal mortality rate reported with maternal chronic hypertension is 2–4 times higher than that of the general population (38), and the increased risk of stillbirth or neonatal death appears to be independent of other possible contributors such as superimposed preeclampsia or fetal growth restriction. The precise blood pressure level at which antihypertensive therapy is indicated during pregnancy in women with chronic hypertension continues to be debated; similarly, it is unknown if strict blood pressure control reduces the risk of stillbirth (38). There also appears to be interaction between chronic hypertension and pregestational diabetes on having a stillbirth and in women with both comorbidities, an even higher risk has been reported (39).

Numerous other medical conditions including systemic lupus erythematosus, renal disease, uncontrolled thyroid disease, and cholestasis of pregnancy have been associated with stillbirth (Table 1). For guidance regarding antenatal fetal surveillance based on anticipated risk of stillbirth, refer to ACOG Practice Bulletin No. 145, *Antepartum Fetal Surveillance*.

Acquired and Inherited Thrombophilias

Antiphospholipid syndrome (APS) is an acquired thrombophilia that has been associated with stillbirth. The diagnosis of APS depends on women meeting laboratory and clinical criteria for the disorder. One of the clinical criteria for APS is history of stillbirth. As such, women with a stillbirth are typically tested for APS (see ACOG Practice Bulletin No. 132, *Antiphospholipid Syndrome*, for details of testing and management). In contrast, inherited thrombophilias have not been associated with stillbirth, and testing for them as part of a stillbirth evaluation is not recommended (40) (Table 2).

Obesity and Gestational Weight Gain

Obesity is defined as a prepregnancy BMI (defined as weight in kilograms divided by height in meters squared) of 30 or greater and is the fastest growing health problem in the United States (41). Obesity in pregnancy is associated with an increased risk of early fetal loss and

Table 1. Estimated Rate of Stillbirth With Maternal or Fetal Conditions

Condition	Estimated Rate of Stillbirth*
All pregnancies	6.4/1000
Diabetes	
Treated with diet (A1)	6–10/1000
Treated with insulin	6–35/1000
Hypertensive disorder	
Chronic hypertension	6–25/1000
Preeclampsia	
without severe features	9–51/1000
with severe features	12–29/1000
Growth restricted fetus	10–47/1000
Multiple gestation	
Twins	12/1000
Triplets	34/1000
Oligohydramnios	14/1000
Late term pregnancy (greater than 41 weeks)	14–40/1000[†]
Previous stillbirth	9–20/1000
Decreased fetal movement	13/1000
Systemic lupus erythematosus	40–150/1000
Renal disease	15–200/1000
Cholestasis of pregnancy	12–30/1000
Advanced maternal age	
35–39 years	11–14/1000
40 years or greater	11–21/1000
Black maternal race	12–14/1000
Maternal age less than 20 years	7–13/1000
Assisted reproductive technology	12/1000
Obesity (prepregnancy)	
BMI equal to or greater than 30 kg/m^2	13–18/1000
Smoking greater than 10 cigarettes per day	10–15/1000

*Rate per 1,000 live births and stillbirths

[†]Data from Rosenstein MG, Snowden JM, Cheng YW, Caughey AB. The mortality risk of expectant management compared with delivery stratified by gestational age and race and ethnicity. Am J Obstet Gynecol 2014;211:660.e1–8.

Adapted from Signore C, Freeman RK, Spong CY. Antenatal testing—a reevaluation: executive summary of a *Eunice Kennedy Shriver* National Institute of Child Health and Human Development workshop. Obstet Gynecol 2009;113:687–701 *and* Fretts RC. Etiology and prevention of stillbirth. Am J Obstet Gynecol 2005;193:1923–35.

Table 2. Stillbirth Recommendations

Recommendation	Grade of Recommendation
Inherited thrombophilias have not been associated with stillbirth, and testing for them as part of a stillbirth evaluation is not recommended.	1C Strong recommendation, low-quality evidence
In women who decline invasive testing, a portion of the placenta, an umbilical cord segment, or internal fetal tissue can be sent for genetic analysis.	1B Strong recommendation, moderate-quality evidence
Microarray analysis, incorporated into the stillbirth workup, improves the test success rate and the detection of genetic anomalies compared with conventional karyotyping.	1A Strong recommendation, high-quality evidence
Genetic evaluation for specific abnormalities should be guided by the clinical history and detected fetal abnormalities.	1C Strong recommendation, low-quality evidence
Evaluation of a stillbirth should include fetal autopsy; gross and histologic examination of the placenta, umbilical cord, and membranes; and genetic evaluation.	1A Strong recommendation, high-quality evidence
Gross and microscopic examination of the placenta, umbilical cord, and fetal membranes by a trained pathologist is the single most useful aspect of the evaluation of stillbirth and is an essential component of the evaluation.	1A Strong recommendation, high-quality evidence
The general examination of the stillborn fetus should be done promptly, noting any dysmorphic features and obtaining measurements of weight, length, and head circumference.	1C Strong recommendation, low-quality evidence
Fetal autopsy should be offered because it is one of the most useful diagnostic tests in determining the cause of death.	1A Strong recommendation, high-quality evidence
Genetic analyses are of sufficient yield that they should be performed in all cases of stillbirth after appropriate parental permission is obtained.	1A Strong recommendation, high-quality evidence
Appropriate history and physical findings should be included in the requisition sent to the laboratory to assist the laboratory personnel to interpret cytogenetic tests.	Best practice
A thorough maternal history should be taken to look for known conditions or symptoms suggestive of those that have been associated with stillbirth.	Best practice
Health care providers should weigh the risks and benefits of each strategy in a given clinical scenario and consider available institutional expertise. Shared decision-making plays an important role in determining the optimal method for delivery in the setting of fetal demise.	Best practice
The results of the autopsy, placental examination, laboratory tests, and cytogenetic studies should be communicated to the involved clinicians and to the family of the deceased infant in a timely manner.	Best practice
Bereavement care should be individualized to recognize bereaved parents' personal, cultural or religious needs.	Best practice
For patients with a previous stillbirth at or after 32 0/7 weeks, once or twice weekly antenatal surveillance is recommended at 32 0/7 weeks or starting at 1–2 weeks before the gestational age of the previous stillbirth. For stillbirth that occurred before 32 0/7 weeks of gestation, individualized timing of antenatal surveillance may be considered.	2C Weak recommendation, low-quality evidence

stillbirth (42). A comprehensive study of five high-income countries found that maternal overweight and obesity (BMI greater than 25) was the most common modifiable risk factor for stillbirth (43). A meta-analysis of 38 studies that included 16,274 stillbirths found that even small increases in maternal BMI were associated with an increased risk of stillbirth. For BMI levels of 20, 25, and 30, absolute risks per 1,000 pregnancies were 4.0 (reference standard), 4.8 (95% CI, 46–51), and 5.9 (95% CI, 55–63), respectively (44). Further,

excessive weight gain was associated with higher risk of stillbirth among obese and morbidly obese women (45). There is some evidence that the obesity-related stillbirth risk increases with gestational age. In one study, the hazard ratio for stillbirth increased from 2.1 at 28–36 weeks to 4.6 at 40 weeks of gestation (46). The reason for this association is likely multifactorial, but obesity is associated with a fivefold increased risk of stillbirth resulting from placental dysfunction. Obesity remains an independent risk factor for stillbirth even after controlling for smoking, gestational diabetes, and preeclampsia (47–49); however, the optimal BMI to minimize stillbirth risk remains unknown (44).

Substance Use

Maternal cocaine, methamphetamine, other illicit drug use, and smoking tobacco, are all significant contributors to abruption and stillbirth (50–54). In a secondary analysis of a case–control study from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Stillbirth Collaborative Research Network, any illicit drug use as detected by biological sampling of the umbilical cord homogenate was associated with an increased risk of stillbirth (OR, 1.94; 95% CI, 1.16–3.27) (55). Smoking is a particularly common risk factor, especially and increasingly in high-income countries. In a recent large systematic review, smoking during pregnancy was significantly associated with a 47% increase in the odds of stillbirth (OR, 1.47; 95% CI, 1.37–1.57, $P<.0001$) (56). The causal relationship of smoking and stillbirth has been established through many studies that demonstrated differential effects based on timing and amount of tobacco exposure.

Exposure to secondhand smoke also increases risk. Women with exposure to secondhand smoke were also at higher risk of stillbirth than never smokers with lower or no secondhand exposure and had comparable risks to some active smokers (57). Timing of exposure is also relevant; smoking during the first trimester is associated with increased risk of stillbirth (adjusted hazard ratio, 2.4; 95% CI, 1.2–4.9) (58). There is also a clear dose-response effect of maternal smoking in pregnancy on risk of stillbirth. Smoking one to nine cigarettes per day was associated with a 9% increased odds of having a stillbirth compared with women who do not smoke in pregnancy (OR, 1.09, 95% CI, 1.09–1.24, $P=.55$, six studies), and smoking 10 or more cigarettes per day was associated with a 52% increase in odds of stillbirth (OR, 1.52; 95% CI, 1.30–1.78, $P<.0001$, seven studies) (56). Quitting smoking between pregnancies is protective. Women who smoked during the first pregnancy but not during the second do not have an increased risk of recurrent stillbirth (OR, 1.02; 95% CI, 0.79–1.30), compared with woman who did not smoke in either pregnancy. The risk among women who smoked during both pregnancies was 1.35 (95% CI, 1.15–1.58) (59).

Assisted Reproductive Technology

Pregnancies achieved by in vitro fertilization (IVF) appear to be associated with an elevated risk (twofold to threefold increase) of stillbirth even after controlling for age, parity, and multifetal gestations (60–63). A more recent study from California for the years 2009–2011 confirms that the stillbirth risk is elevated at 5.5 per 1,000 (64). Whether this is related to the procedures themselves or to unmeasured confounding variables associated with underlying causes of infertility is less clear. Couples with a waiting time to pregnancy of 1 year or more and women who became pregnant after non-IVF assisted reproductive technology had a risk for stillbirth similar to that of fertile couples and a lower risk than women who became pregnant after IVF or intracytoplasmic sperm injection, which indicates that the increased rate of stillbirth risk may be a result of the IVF or intracytoplasmic sperm injection and not the underlying infertility (62).

Late-Term and Postterm Pregnancies

In a Cochrane review of 30 RCTs of 12,479 women that compared expectant management with induction of labor in term and postterm pregnancies, induction of labor was associated with a decreased risk of perinatal death and cesarean delivery (65). Based on these and other observational data, induction of labor for an indication of late-term and postterm pregnancy is recommended after 42 0/7 weeks of gestation and can be considered at or after 41 weeks 0/7 days of gestation (66). Estimates of the risk of stillbirth after 41 weeks differ by race and ethnicity and range from 14–40 per 1,000 live births (67). For the California population overall from 1997–2006, mortality risks of stillbirth and neonatal death were equivalent at 38 weeks of gestation, but at later gestational ages the mortality risk of expectant management exceeded that of delivery with a mortality risk of 17.6 per 10,000 compared with 10.8 per 10,000 ongoing pregnancies at 42 weeks of gestation (68). The RR of stillbirth in this cohort was 2.9 (95% CI, 2.6–3.2) at 41 weeks and 5.1 (95% CI, 4.4–6.0) at 42 weeks, when compared with a referent stillbirth rate at 37 weeks (68).

Potential Causes of Stillbirth

The study of specific causes of stillbirth has been hampered by the lack of uniform protocols to evaluate and classify stillbirths and by decreasing autopsy rates. In most cases, stillbirth certificates are filled out before a full postnatal investigation has been completed and amended death certificates are rarely filed when additional information from the stillbirth evaluation emerges. In any specific case, it may be difficult to assign a definite cause to a stillbirth. A significant proportion of stillbirths remains unexplained even after a thorough evaluation (69).

Fetal Growth Restriction

Fetal growth restriction is associated with a significant increase in the risk of stillbirth. The most severely affected fetuses (weight less than the 2.5th percentile) are at greatest risk (70, 71). The cumulative risk of stillbirth is approximately 1.5% at fetal weights less than the 10th percentile, and the risk increases to 2.5% at less than the 5th percentile for gestational age (72, 73). Similarly, using data from all births in the United States, investigators demonstrated increased risk of stillbirth with increasing severity of growth restriction. The risk of stillbirth was highest among fetuses estimated to be less than the 3rd percentile for growth (58.0 per 10,000 at risk), decreased for those less than the 5th percentile (43.9 per 10,000 at risk) and was the lowest for those less than the 10th percentile (26.3 per 10,000 at risk) (71). Fetal growth restriction is associated with some fetal aneuploidies, fetal infection, maternal smoking, hypertension, autoimmune disease, obesity, and diabetes, which also modify the risk of stillbirth.

Placental Abruption

Placental abruption is identified as the cause of stillbirth in 5–10% of cases (69). Maternal cocaine and other illicit drug use, and smoking tobacco, are all significant contributors to abruption and stillbirth (50–53). If abruption occurs in the preterm fetus or involves a larger surface area of the placenta (74), it is more likely to cause stillbirth. The rates of abruption appear to be increasing (75). Hemodynamically significant fetomaternal hemorrhage in the absence of placental abruption is a rare cause of stillbirth and occurs mainly in unusual scenarios, such as chorioangioma or choriocarcinoma (76, 77).

Chromosomal and Genetic Abnormalities

An abnormal karyotype can be found in approximately 6–13% of stillbirths (69, 78–80). The rate of karyotypic abnormalities exceeds 20% in fetuses with anatomic abnormalities or in those with growth restriction, but the rate of chromosomal anomalies found in normally formed fetuses was found to be 4.6% in one large series (80). If an abnormal karyotype is found in association with stillbirth, the most common abnormalities are trisomy 21 (31%), monosomy X (22%), trisomy 18 (22%), and trisomy 13 (8%) (80).

Karyotypic analysis underestimates the contribution of genetic abnormalities to stillbirth because in up to 50% of karyotype attempts, cell culture is unsuccessful (79). One strategy to increase the yield of cell culture is to perform chorionic villi sampling or amniocentesis before the delivery. In a large study in the Netherlands, invasive testing had a much greater tissue culture rate (85%) than fetal tissue sampling after birth (28%) (80). In women who decline invasive testing, a portion of the placenta, an umbilical cord segment, or internal fetal tissue can be sent for genetic analysis (Fig. 2).

Microarray analysis not only detects aneuploidy but also detects copy number variants (smaller deletions and duplications) that are not detectable by karyotype. As compared to karyotype analysis, microarray analysis increased the diagnosis of a genetic cause to 41.9% in all stillbirths, 34.5% in antepartum stillbirths, and 53.8% in stillbirths with anomalies (81). Microarray analysis was more likely than karyotype analysis to provide a genetic diagnosis, primarily because of its success with nonviable tissue, and it was especially valuable in analyses of stillbirths with congenital anomalies or when karyotype results could not be obtained. Thus, microarray analysis, incorporated into the stillbirth workup, improves the test success rate and the detection of genetic anomalies compared with conventional karyotyping (82). Microarrray is the preferred method of evaluation for these reasons but, due to cost and logistic concerns, karyotype may be the only method readily available for some patients. In the future, whole exome sequencing or whole genome sequencing may be part of the stillbirth workup, but it is not currently part of the standard evaluation.

Confined placental mosaicism in which the karyotype of the fetus is euploid despite an abnormal cell line in the placenta also has been associated with an increased risk of stillbirth, but currently it is not part of standard testing (83). Autosomal dominant disorders caused by spontaneous mutations (eg, skeletal dysplasias) or inherited parental mutations leading to long QT syndrome may contribute to stillbirth (84, 85). However, routine assessments for single gene defects and microdeletions currently are limited because it is unlikely that any single gene defect will be responsible for a significant proportion of stillbirths. Genetic evaluation for specific abnormalities should be guided by the clinical history and detected fetal abnormalities. Approximately 20% of stillborn fetuses have dysmorphic features or skeletal abnormalities and 15–20% have a major malformation (78, 86).

Infection

Infection is associated with approximately 10–20% of stillbirths in developed countries and a greater percentage in developing countries (69, 87). In developed countries, infection accounts for a greater percentage of preterm stillbirths than of term stillbirths (69, 88). Infectious pathogens may result in stillbirth by producing direct fetal infection, placental dysfunction, severe maternal illness, or by stimulating spontaneous preterm birth.

Placental and fetal infections originate from either ascending (eg, group B streptococcus or *Escherichia coli*) or hematogenous spread of agents such as *Listeria monocytogenes* or syphilis. Viral infections associated with stillbirth include cytomegalovirus, parvovirus, and Zika. Serology for toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus are not included because they are of unproven benefit and not recommended (89).

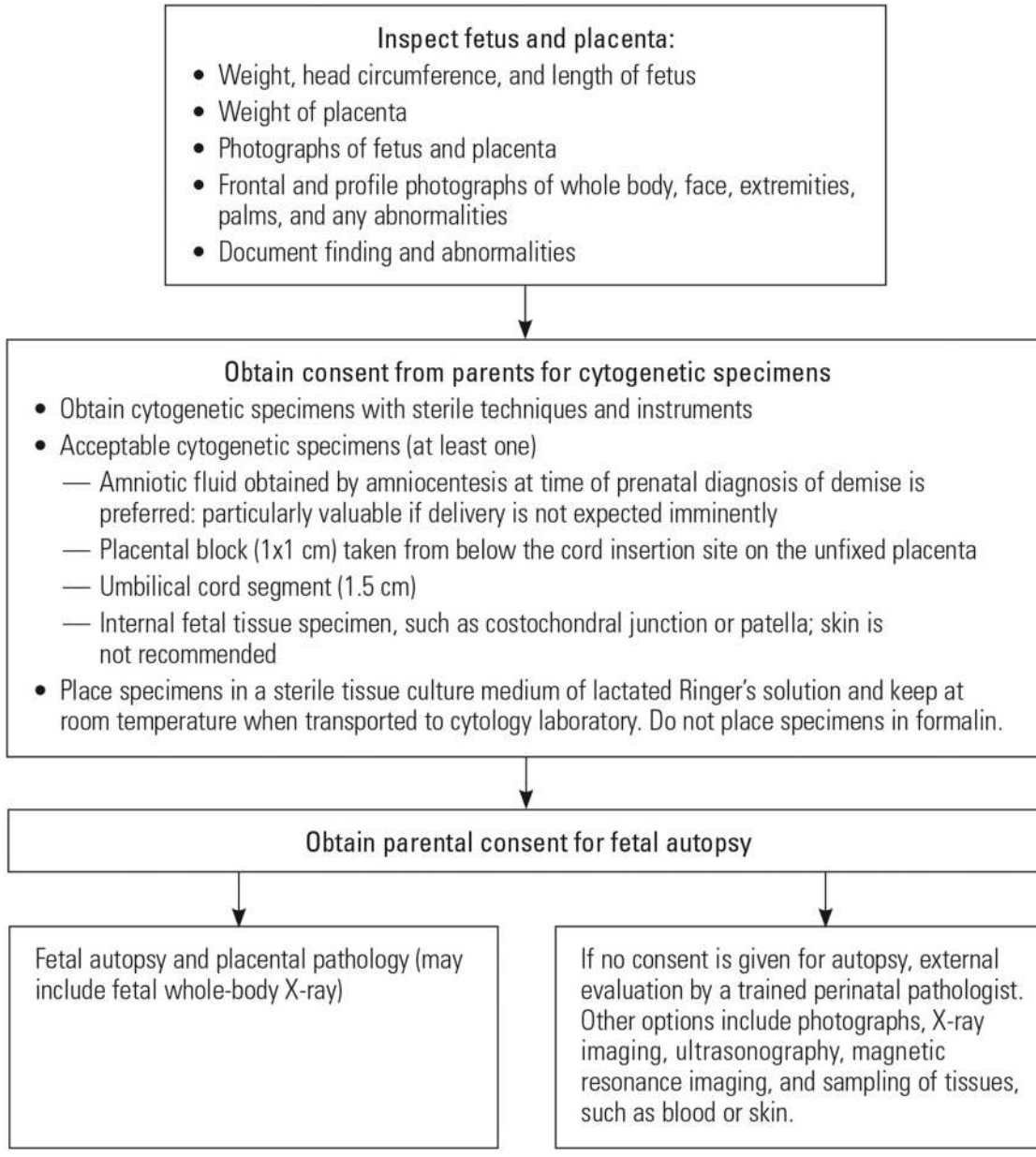

Figure 2. Fetal and placental evaluation

Umbilical Cord Events

Umbilical cord abnormalities account for approximately 10% of stillbirths but this diagnosis should be made with caution (69). In a cohort–control study of almost 14,000 deliveries, single nuchal cords were present at birth in 23.6% of deliveries and multiple nuchal cords in 3.7%. Single or multiple nuchal cords were not associated with an increased risk of stillbirth in this cohort (90). The criteria for considering a cord abnormality to be a cause of death were rigorous in the Stillbirth Collaborative Research Network and included vasa previa, cord entrapment, and evidence of occlusion and fetal hypoxia, prolapse, or stricture with thrombi (69). Nuchal cord alone was not considered a cause of death. In addition, other causes of stillbirth should be excluded.

Clinical Considerations and Management

► ***What are the essential components of a stillbirth evaluation?***

Evaluation of a stillbirth should include fetal autopsy; gross and histologic examination of the placenta, umbilical cord, and membranes; and genetic evaluation (91). An algorithm for evaluation is provided in Figure 2. Specific aspects of the evaluation are outlined as follows and in Figure 3.

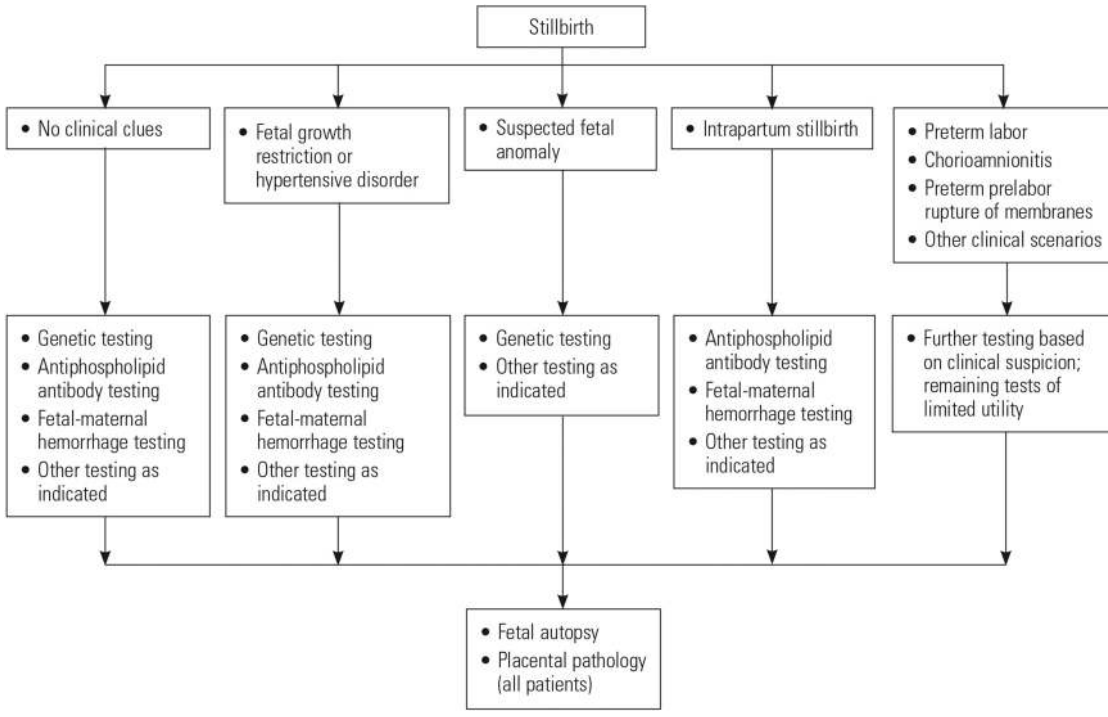

Figure 3. Evaluation of stillbirth based on test utility in a variety of clinical scenarios. (Adapted from Page JM, Christiansen-Lindquist L, Thorsten V, Parker CB, Reddy UM, Dudley DJ, et al. Diagnostic Tests for Evaluation of Stillbirth: Results From the Stillbirth Collaborative Research Network. Obstet Gynecol 2017;129:699–706.)

Examination of the Placenta

Gross and microscopic examination of the placenta, umbilical cord, and fetal membranes by a trained pathologist is the single most useful aspect of the evaluation of stillbirth and is an essential component of the evaluation (91, 92). Gross evaluation may reveal conditions such as abruption, umbilical cord thrombosis, velamentous cord insertion, and vasa previa. Placental evaluation may also provide information regarding infection, genetic abnormalities, and anemia. Examination of the placental vasculature and membranes can be particularly revealing in stillbirths that occur as part of a multifetal gestation. Chorionicity should be established and vascular anastomoses identified.

Umbilical cord knots or tangling should be noted but interpreted with caution, as cord entanglement occurs in approximately 25% of normal pregnancies and most true knots are found after live births. Corroborating evidence should be sought before concluding that a cord accident is the likely cause of death (eg, evidence of cord occlusion and hypoxia on perinatal postmortem examination and histologic examination of the placenta and umbilical cord). The minimal histologic criteria for considering a diagnosis of cord accident should include vascular ectasia and thrombosis in the umbilical cord, chorionic plate, and stem villi. In addition to the previous findings, for a probable diagnosis, a regional distribution of avascular villi or villi showing stromal karyorrhexis is suggested (93).

Examination of the Stillborn Fetus

The general examination of the stillborn fetus should be done promptly, noting any dysmorphic features and obtaining measurements of weight, length, and head circumference (94–96). Foot length may be especially useful before 23 weeks of gestation to ascertain gestational age. Photographs of the whole body (unclothed); frontal and profile views of the face, extremities, and palms; and close-up photographs of specific abnormalities are vital for subsequent review and consultation with a specialist, particularly if no geneticist is available at the institution.

Fetal autopsy should be offered because it is one of the most useful diagnostic tests in determining the cause of death. The yield is increased when dysmorphic features, inconsistent growth measurements, anomalies, hydrops, or growth restriction are present. If families are uncomfortable with a complete autopsy, other options such as partial autopsy, gross examination by a trained pathologist, ultrasonography and especially magnetic resonance imaging are particularly useful. Parents should be given the opportunity to hold the baby and perform cultural or religious activities before the autopsy. Whole-body X-ray with anterior–posterior and lateral views may reveal an unrecognized skeletal abnormality or further define a grossly apparent deformity.

When a full autopsy is performed, it should follow published guidelines and protocols for perinatal autopsy (97, 98). These include measurements to establish

gestational age, such as foot length and body weight. Recommendations also include an estimation of the interval between death and delivery, identification of intrinsic abnormalities and developmental disorders, and investigation for evidence of infection. It is preferable to use a pathologist who is experienced in perinatal autopsy and to have a physician who is experienced in genetics and dysmorphology examine the fetus. The clinician should communicate the obstetric and pertinent medical history to the pathology team and request any tissue collection that may be needed for additional analysis.

Fetal Laboratory Studies

Genetic analyses are of sufficient yield that they should be performed in all cases of stillbirth after appropriate parental permission is obtained (80). Karyotype or microarray are of higher yield if the fetus displays dysmorphic features, inconsistent growth measurements, anomalies, hydrops, or growth restriction (81). Comparative genomic hybridization or single nucleotide probe and copy number probe microarrays provide almost the same information as karyotype plus they detect abnormalities in smaller regions of chromosomes that are missed by traditional karyotyping. Single nucleotide probe arrays also can detect uniparental disomy and consanguinity. Fetal karyotype is important if a parent carries a balanced chromosomal rearrangement (eg, translocation or inversion) or has a mosaic karyotype.

Acceptable cytogenetic specimens include amniotic fluid and a placental block taken from below the cord insertion site that includes the chorionic plate, an umbilical cord segment, or an internal fetal tissue specimen that thrives under low-oxygen tension such as costochondral or patellar tissue. Fetal skin is suboptimal (see Fig. 1) (99–101). Amniocentesis for fetal karyotyping has the highest yield and is particularly valuable if delivery is not expected imminently (80). Appropriate history and physical findings should be included in the requisition sent to the laboratory to assist the laboratory personnel to interpret cytogenetic tests. Cost of various genetic analyses may affect patient decision making at the time of stillbirth evaluation, and efforts should be made to communicate information about anticipated cost whenever possible.

Maternal Evaluation

A thorough maternal history should be taken to look for known conditions or symptoms suggestive of those that have been associated with stillbirth (Table 3). In addition to the medical and obstetric history, including exposures (eg, medications and viral infections), a family history with a three-generation pedigree including stillborn infants should be reviewed. Any pertinent information in the maternal or paternal pedigree should be documented and investigated further. Recurrent pregnancy losses and the presence of live born individuals with developmental delay or structural anomalies may be clues to single-gene disorders. Consanguinity should be identified because of the increased possibility of severe autosomal recessive disorders. A detailed history of arrhythmias and sudden death (including sudden infant death syndrome) should be ascertained, because prolonged QT syndrome may be associated with stillbirth.

Relevant original medical records and documentation should be obtained whenever possible. The gestational age by last menstrual period, maternal examinations, laboratory data, and ultrasound examination should be recorded for correlation with the physical examination of the neonate. Possible nongenetic causes, such as infection, placental abruption, and umbilical cord abnormality also should be considered.

Although fetomaternal hemorrhage is an uncommon cause of stillbirth, Kleihaur-Betke testing could be falsely elevated after delivery; therefore, testing for significant fetomaternal hemorrhage either with a Kleihaur-Betke or flow cytometry test should be conducted as soon as possible after the diagnosis of stillbirth (102).

Antiphospholipid syndrome testing is recommended in many stillbirths, especially when accompanied by fetal growth restriction, severe preeclampsia, or other evidence of placental insufficiency. Laboratory testing is performed by testing for lupus anticoagulant as well as immunoglobulin G and immunoglobulin M for both anticardiolipin and β_2-glycoprotein antibodies. A moderate to high immunoglobulin G phospholipid or immunoglobulin M phospholipid titer (greater than 40 immunoglobulin M phospholipid or immunoglobulin G phospholipid, or greater than 99th percentile) is considered positive but must be confirmed with repeat testing after 12 weeks. Elevated levels of anticardiolipin and anti-β_2-glycoprotein-I antibodies are associated with a threefold to fivefold increased odds of stillbirth, which supports testing for antiphospholipid antibodies in cases of otherwise unexplained stillbirth (103). However, testing for inherited thrombophilias is not recommended (40).

The percentage of cases in which the various components of the stillbirth evaluation were considered useful to establish a cause of stillbirth in the Stillbirth Collaborative Research Network study of 512 stillbirths that underwent a complete evaluation was as follows: 64.6% placental pathology (95% CI, 57.9–72.0), 42.4% fetal autopsy (95% CI, 36.9–48.4), 11.9% genetic testing by karyotype or microarray (95% CI, 9.1–15.3), 11.1% testing for antiphospholipid antibodies (95% CI, 8.4–14.4), 6.4% fetal–maternal hemorrhage (95% CI, 4.4–9.1), 1.6% glucose screen (95% CI, 0.7–3.1), 0.4% parvovirus (95% CI, 0.0–1.4), and 0.2% syphilis (95% CI, 0.0–1.1). The utility of the tests varied by clinical presentation, which suggests a customized approach for each patient. The most useful tests were placental pathology and fetal autopsy followed by genetic testing and testing for antiphospholipid antibodies. Further testing is indicated based on the results of the

Table 3. Elements of a Stillbirth Evaluation

Key Components	Details	Comments
Patient History	Family history	
	• Recurrent spontaneous abortions	
	• Venous thromboembolism	
	• Congenital anomaly or chromosomal abnormalities	
	• Hereditary condition or syndrome	
	• Developmental delay	
	• Consanguinity	
	Maternal history	
	• Previous venous thromboembolism	
	• Diabetes mellitus	
	• Chronic hypertension	
	• Thrombophilia	
	• Systemic lupus erythematosus	
	• Autoimmune disease	
	• Epilepsy	
	• Severe anemia	
	• Heart disease	
	• Tobacco, alcohol, drug or medication use	
	Obstetric history	
	• Recurrent miscarriages	
	• Previous child with anomaly, hereditary condition, or growth restriction	
	• Previous gestational hypertension or preeclampsia	
	• Previous gestational diabetes mellitus	
	• Previous placental abruption	
	• Previous fetal demise	
	Current pregnancy	
	• Maternal age	
	• Gestational age at stillbirth	
	• Medical conditions complicating pregnancy	
	○ Cholestasis	
	• Pregnancy weight gain and body mass index	

(*continued*)

Table 3. Elements of a Stillbirth Evaluation (*continued*)

Key Components	Details	Comments
	• Complications of multifetal gestation, such as twin–twin transfusion syndrome, twin reversed arterial perfusion syndrome, and discordant growth	
	• Placental abruption	
	• Abdominal trauma	
	• Preterm labor or rupture of membranes	
	• Gestational age at onset of prenatal care	
	• Abnormalities seen on an ultrasound image	
	• Infections or chorioamnionitis	
Fetal autopsy	If patient declines, external evaluation by a trained perinatal pathologist. Other options include photographs, X-ray imaging, ultrasonography, magnetic resonance imaging, and sampling of tissues, such as blood or skin.	Provides important information in approximately 30% of cases
Placental examination	Includes evaluation for signs of viral or bacterial infection. Discuss available tests with pathologist.	Provides additional information in 30% of cases. Infection is more common in preterm stillbirth (19% vs. 2% at term)
Fetal karyotype/microarray	Amniocentesis before delivery provides the greatest yield. Umbilical cord proximal to placenta if amniocentesis declined	Abnormalities found in approximately 8% of cases
Maternal evaluation at time of demise	• Fetal–maternal hemorrhage screen: Kleihauer-Betke test or flow cytometry for fetal cells in maternal circulation	Routine testing for inherited thrombophilias is not recommended. Consider in cases with a personal or family history of thromboembolic disease.
	• Syphilis	
	• Lupus anticoagulant	
	• Anticardiolipin antibodies	
	• β_2 glycoprotein antibodies	
In selected cases	Indirect Coombs	If not performed previously in pregnancy.
	Glucose screening (oral glucose tolerance test, hemoglobin A_{1C})	In the large for gestational age baby
	Toxicology screen	In cases of placental abruption or when drug use is suspected

postmortem examination and placental histology, as well as the clinical circumstances accompanying the stillbirth (91) (see Fig. 3, Evaluation of Stillbirth).

► ***What are the options for management of the current pregnancy after confirmation of a diagnosis of stillbirth?***

Methods of Delivery

The method and timing of delivery after a stillbirth depend on the gestational age at which the death occurred, maternal obstetric history (eg, previous hysterotomy), and maternal preference. Although most patients desire prompt delivery, the timing of delivery is not critical; coagulopathies associated with prolonged fetal retention are uncommon.

Options for delivery of the stillborn fetus typically include dilation and evacuation or induction of labor. In the second trimester, dilation and evacuation can be offered if an experienced health care provider is available, although patients should be counseled that dilation and evacuation may limit efficacy of autopsy for the detection of macroscopic fetal abnormalities, and often precludes seeing or holding the fetus after removal. On the other hand, women undergoing induction of labor, especially early in the second trimester, are at high risk of requiring a dilation and curettage for removal of the placenta after delivery of the fetus. In addition, induction of labor for pregnancies with a fetal demise between 14 weeks and 24 weeks of gestation has been associated with an increased risk of maternal morbidity (predominantly infection morbidity that requires intravenous antibiotics) when compared with surgical uterine evacuation (104). Induction of labor has also been demonstrated to be less effective and to have higher complication rates than dilation and evacuation between 13 weeks and 24 weeks of gestation with an adjusted risk ratio of 8.5 (95% CI, 3.7–19.8) (105). Health care providers should weigh the risks and benefits of each strategy in a given clinical scenario and consider available institutional expertise. Shared decision making plays an important role in determining the optimal method for delivery in the setting of fetal demise.

Appropriate methods for labor induction vary based on gestational age at the time of fetal demise. Much of the data for management of fetal demise are extrapolated from randomized trials that evaluated optimal methods for second trimester pregnancy termination. Before 28 weeks of gestation, vaginal misoprostol appears to be the most efficient method of induction, regardless of cervical Bishop score (106, 107), although high-dose oxytocin infusion also is an acceptable choice (108–111). A meta-analysis of 14 randomized controlled trials that evaluated methods of induction for second and third trimester stillbirth demonstrated that both vaginal and oral misoprostol regimens were 100% effective in achieving uterine evacuation within 48 hours (112). Dose regimens and frequency of administration differed in the included trials, which makes direct comparisons of dose strategy challenging. Based on limited evidence, before 28 weeks of gestation, typical dosages for misoprostol are 400–600 micrograms vaginally every 3–6 hours. Doses less than 400 micrograms have decreased efficacy (113). After 28 weeks of gestation, induction of labor should be managed according to usual obstetric protocols.

There is high-quality evidence to support the use of mifepristone plus misoprostol for management of pregnancy loss before 20 weeks when compared to misoprostol alone (114). Data regarding the use of mifepristone as an adjunct to misoprostol for pregnancy loss from 24–28 weeks are more limited (115–117). Mifepristone (either 200 or 600 mg orally) can be used as an adjunct to misoprostol for induction of labor in the setting of stillbirth and reduces the time to delivery when compared with misoprostol alone. However, it does not appear to increase overall efficacy of induction (115). When available, mifepristone can be administered 24–48 hours before initiation of induction with misoprostol.

Both induction of labor and dilation and evacuation remain options for women with a previous hysterotomy. In a population-based case–control study of 611 stillbirths, induction of labor resulted in vaginal delivery for 91% (41 of 45) of women with a history of cesarean delivery with two cases of uterine rupture (118). Although induction of labor is preferred rather than cesarean delivery in the setting of fetal demise, the presence of a previous hysterotomy modifies management. Several studies have evaluated the use of misoprostol at a dosage of 400 micrograms every 6 hours in women with a stillbirth between 24 and 28 weeks of gestation and a previous uterine scar (119, 120). Available evidence from randomized trials supports the use of vaginal misoprostol as a medical treatment to terminate nonviable pregnancies before 24 weeks of gestation (110). Further research is required to assess effectiveness and safety, optimal route of administration, and dose, especially in women between 24 weeks and 28 weeks of gestation in whom lower doses of misoprostol (200 micrograms per dose) may be preferred (113). Women with a previous hysterotomy and fetal demise after 28 weeks of gestation should undergo induction of labor per standard obstetric protocols for trial of labor after cesarean (see ACOG Practice Bulletin No. 205, *Vaginal Birth After Cesarean Delivery*) rather than misoprostol administration.

In patients after 28 weeks of gestation with a previous hysterotomy, cervical ripening with a transcervical Foley catheter has been associated with uterine rupture rates comparable to spontaneous labor (121), and this may be a helpful adjunct in patients with an unfavorable cervical examination. Therefore, based on

limited data in patients with one previous low transverse cesarean delivery, trial of labor remains a favorable option. There are limited data to guide clinical practice in a patient with a previous classical cesarean delivery or multiple previous cesarean deliveries, and the delivery plan should be individualized based on individual circumstances and patient preference. In general, cesarean delivery for fetal demise should be reserved for unusual circumstances because it is associated with potential maternal morbidity without any fetal benefit. In women with an increased risk of uterine rupture (eg, history of classical hysterotomy or transfundal surgery), repeat cesarean delivery is a reasonable option. Women with an increased risk of uterine rupture who opt for induction of labor should do so with an understanding of the increased risk, and health care providers need to be attuned to signs and symptoms of uterine rupture throughout the labor course.

► ***What support services and clinical counseling should be offered to the patient with a stillbirth?***

Patient support should include emotional support and clear communication of test results. Bereavement care should be individualized to recognize bereaved parents' personal, cultural, or religious needs. Other components of bereavement care after a stillbirth include good communication; shared decision making;

Table 4. Principles of Bereavement Care

Individualized bereavement care	Bereavement care should be individualized to recognize bereaved parents' personal, cultural, or religious needs. Time needs to be spent with bereaved parents to gain an understanding of their wishes.
Good communication	Communication with bereaved parents should be clear and honest. The term "your baby or babies" should be used in conversation; terms such as fetus, embryo, or spontaneous abortion should be avoided.
Shared decision making	Parents should be provided with full information into any important decisions to be made regarding themselves or their baby (babies). Parents should be given adequate time to consider all options available to them.
Recognition of parenthood	Recognition of parenthood and the role of memory making is vitally important as it is thought to assist with the actualization of grief and the slow transition of the parents' relationship with their baby from one of presence to one of memory. One of the greatest regrets that bereaved parents have reported is the lack of memories of their baby.
Acknowledging a partner's and families' grief	Recognition that a partner's and family's grief can be as profound as that of the mother and that their need for support should be considered and met. Support services should be made available and resources given to the parents and their families.
Acknowledging that grief is individual	Recognition of the grief journey and that all bereaved parents will handle and react differently to grief. The intensity and duration of grief will be different. Health professionals should be made aware that different grief responses are normal and that there is no perfect way to grieve.
Awareness of burials, cremation, and funerals	All babies, no matter what gestation, should be treated with respect at all times. Options for burial, cremation, taking baby home, home funerals, and conventional funerals should be discussed before the baby is born, if possible, to give as much time to organize, consider, and for all options to remain open. Health professionals should be aware of burial, cremation, and funeral options available in their local area.
Ongoing emotional and practical support	Bereaved parents should be provided with information and referrals to both professional support and peer-to-peer support services such as First Candle. The concept of seeking support (professional or peer) should be normalized for bereaved parents and encouraged. Bereaved parents who access support services report that they feel their grief was heard, understood, and validated have greater prospects of hope for the future.
Health professionals trained in bereavement care	All health care professionals who interact with bereaved parents should aim to attend professional development opportunities and to be familiar with the principles of bereavement care.
Health professionals with access to self-care	It is ok not to be ok after the death of a baby. All staff who care for bereaved parents before, during, and after the death of a baby will be affected emotionally. Health professionals are in the "helping" profession and when they cannot help this can bring up difficult emotions. Staff should have good access to information about effective self-care.

Modified from Sands Australian Principles of Bereavement Care: Miscarriage, Stillbirth and Newborn Death, 1st edition, May 2018.

recognition of parenthood; acknowledgement of a partners' and families' grief; acknowledgement that grief is individual; awareness of burials, cremation, and funerals; ongoing emotional and practical support; health professionals trained in bereavement care; and health professionals with access to self-care (122) (Table 4). Referral to a bereavement counselor, peer support group, or mental health professional may be advisable for management of grief and depression. Feelings of guilt or anger in parents who have experienced a stillbirth are common and may be magnified when there is an abnormal child or a genetic defect. However, some parents may welcome discussion and find relief in autopsy results. The results of the tests are important even when no specific diagnosis is identified (123). The results of the autopsy, placental examination, laboratory tests, and cytogenetic studies should be communicated to the involved clinicians and to the family of the deceased infant in a timely manner. If there was no growth of the fetal chromosomes (or these were not obtained), further consultation with a genetic or maternal–fetal medicine subspecialist is advised to discuss the need for parental chromosomal testing. A copy of the results of the tests and a list of diagnoses excluded should be provided to the patients if desired.

► ***For the patient with a history of an unexplained stillbirth in a previous pregnancy, how should clinical management be altered in subsequent pregnancies?***

Data on management of pregnancies after an unexplained stillbirth are scarce. Women should be encouraged to minimize the risk of stillbirth attributable to modifiable risk factors (eg, optimize glycemic control in the setting of diabetes). However, a 2018 Cochrane review found insufficient evidence to inform clinical practice regarding effective interventions to improve care for women with a history of stillbirth (124).

Risk of Stillbirth Recurrence Counseling

The evidence surrounding the recurrence risk of stillbirth remains controversial and limited (14). Counseling can be hampered by insufficient information regarding the etiology of the previous stillbirth. In many cases, the previous stillbirth may be unexplained despite a thorough evaluation. In a systematic review and meta-analysis of 13 cohort and three case–control studies, increased risk of stillbirth was found among women with a history of any stillbirth (2.5%) compared with those with a history of live birth (0.4%) (pooled OR, 4.83; 95% CI, 3.77–6.18). In this meta-analysis, the authors were unable to pool the studies that specifically evaluated the risk of stillbirth in the setting of previous unexplained stillbirth. Two studies included in the systematic review reported adjusted risks for stillbirth in a subsequent pregnancy after previous unexplained stillbirth of 3.11 (95% CI, 0.72–13.50) and 1.00 (95% CI, 0.23–4.30) (125, 126). A retrospective analysis reported adjusted risks for unexplained stillbirth after one previous stillbirth of 4.18 (95% CI, 1.36–12.89) (127).

When specific risks for stillbirth are identified, the risk of recurrence may be better quantified (Table 1). Rates of recurrent fetal loss are higher in women with medical complications such as diabetes or hypertension or in those with obstetric problems with a significant recurrence risk, such as placental abruption. Despite reassurances, the patient is likely to be anxious and to require extra support (128).

Antepartum Surveillance

There are little data to guide the treating clinician in the antepartum surveillance of a patient who had a previous unexplained stillbirth. Compared with women whose first infant was live born, those with a previous stillborn infant are 2.5 times (95% CI, 1.4–4.7) more likely to have a subsequent stillbirth (16). The risk of recurrent stillbirth may be increased as high as 10-fold depending on maternal race and characteristics of the previous stillbirth, such as etiology, gestational age, and presence of fetal growth restriction (129). Using maternal linked cohort data, stillbirth occurred in 22.7 per 1,000 women with a previous stillbirth compared with 4.7 per 1,000 for those without such a history (130). The etiology of a previous stillbirth also affects the ability of antenatal testing to prevent recurrences. However, for many cases of stillbirth the etiology is unknown (131).

For stillbirths associated with specific conditions, such as hypertension or diabetes, the fetal surveillance should be part of the recommended management guidelines for such conditions. For patients with a previous stillbirth at or after 32 0/7 weeks, once or twice weekly antenatal surveillance is recommended at 32 0/7 weeks or starting at 1–2 weeks before the gestational age of the previous stillbirth. For prior stillbirth that occurred before 32 0/7 weeks of gestation, individualized timing of antenatal surveillance may be considered. However, this approach is associated with potential morbidity and cost: rates of delivery for abnormal or equivocal testing were 16.3% at or before 39 weeks of gestation and 1% before 36 weeks of gestation. Similarly, the authors of one study estimate that antenatal testing before 37 weeks of gestation results in a 1.5% rate of iatrogenic prematurity for intervention based on false-positive test results (132). The excess risk of infant mortality because of late preterm birth is 8.8 per 1,000 live births at 32–33 weeks of gestation and 3 per 1,000 at 34–36 weeks of gestation (133), and this must be considered in any strategy that may lead to iatrogenic late preterm birth.

Fetal Kick Counting for Women with History of Unexplained Stillbirth

Multiple studies have demonstrated that women who report decreased fetal movement are at increased risk for adverse perinatal outcomes (134). Although fetal kick counting is an inexpensive test of fetal well-being,

evidence of its effectiveness in preventing stillbirth remains uncertain (135, 136). One study demonstrated that a combination of providing uniform information to patients and improving standardized guidelines for health care providers in the management of decreased fetal movement was associated with a reduction in stillbirth rates (137). However, a large randomized study of fetal movement awareness with a primary outcome of stillbirth did not demonstrate a reduction in stillbirth rates, and there was an observed increase in interventions such as inductions and hospital admissions (138). There are insufficient data to make specific recommendations regarding fetal kick counts. Best practices regarding fetal kick counting seems to involve encouragement of awareness of fetal movement patterns, being attentive to the complaint of reduced fetal movements, addressing the complaint in a systematic way, and the use of shared decision making to employ interventions safely (139).

Timing of Delivery

The decision to proceed with early delivery to prevent stillbirth must incorporate an understanding of the increased risks of maternal and neonatal complications compared with the potential benefits. Risks of pregnancy continuation will be variable and largely dependent on underlying maternal and fetal comorbidities in the current pregnancy. Deliveries before 39 weeks of gestation are associated with an increased risk of admission to neonatal special care units for respiratory complications and other neonatal morbidities; however, maternal anxiety with a history of stillbirth should be considered and may warrant an early term delivery (37 0/7 weeks to 38 6/7 weeks) in women who are educated regarding, and accept, the

Box 1.
Management of Subsequent Pregnancy After Stillbirth

Prepregnancy or Initial Prenatal Visit

Detailed medical and obstetric history
Evaluation and workup of previous stillbirth
Determination of recurrence risk
Smoking cessation
Weight loss in obese women (prepregnancy only)
Genetic counseling if family genetic condition exists
Diabetes screen
Acquired thrombophilia testing: lupus anticoagulant as well as IgG and IgM for both anticardiolipin and β2-glycoprotein antibodies
Support and reassurance

First Trimester

Dating ultrasonography
First-trimester screen: pregnancy-associated plasma protein A, human chorionic gonadotropin, and nuchal translucency* or cell-free fetal DNA testing
Support and reassurance

Second Trimester

Fetal sonographic anatomic survey at 18–20 weeks
Offer genetic screening if not performed in the first trimester or single marker alpha fetoprotein if first trimester screening already performed
Support and reassurance

Third Trimester

Sonographic screening for fetal growth restriction after 28 weeks
Antepartum fetal surveillance starting at 32 weeks of gestation or 1–2 weeks earlier than previous stillbirth
Support and reassurance

Delivery

Planned delivery at 39 0/7 weeks of gestation or as dictated by other maternal or fetal comorbid conditions. In cases of severe patient anxiety, where there is a preference to proceed with early term delivery (37 0/7 weeks to 38 6/7 weeks) to prevent recurrent stillbirth, such decisions must incorporate the understanding of the increased risks of neonatal complications with early term delivery compared with the potential benefit.

*Provides risk modification but does not alter management.

(Adapted from Reddy UM. Prediction and prevention of recurrent stillbirth. Obstet Gynecol 2007;110:1151–64.)

associated neonatal risks. Ultimately, actual care and delivery interventions should be based on all potential aspects of the maternal and fetal conditions, as well as the risks and benefits associated with the suggested timing of delivery. When the suggested timing of delivery occurs during early term periods, timing of delivery must balance the maternal and newborn risk of early term delivery with the risks of further continuation of pregnancy. Amniocentesis for the determination of fetal lung maturity generally should not be used to guide the timing of delivery. Details of pregnancy management recommendations for women with a previous stillbirth are listed in Box 1.

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Society for Maternal–Fetal Medicine Grading System: Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Recommendations

Obstetric Care Consensus documents will use the Society for Maternal-Fetal Medicine's grading approach: http://www.ajog.org/article/S0002-9378%2813%2900744-8/fulltext. Recommendations are classified as either strong (Grade 1) or weak (Grade 2), and quality of evidence is classified as high (Grade A), moderate (Grade B), and low (Grade C)*. Thus, the recommendations can be one of the following six possibilities: 1A, 1B, 1C, 2A, 2B, 2C.

Grade of Recommendation	Clarity of Risk and Benefit	Quality of Supporting Evidence	Implications
1A. Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	Consistent evidence from well performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Strong recommendations, can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1B. Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation, and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C. Strong recommendation, low quality evidence	Benefits appear to outweigh risk and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or from randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
2A. Weak recommendation, high quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Weak recommendation, best action may differ depending on circumstances or patients or societal values.
2B. Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances.
2C. Weak recommendation, low quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or from randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation, other alternatives may be equally reasonable.
Best practice	Recommendation in which either (i) there is enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize), or (ii) recommendation to contrary would be unethical.		

Modified from Grading guide. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Available at: http://www.uptodate.com/home/grading-guide. Retrieved October 9, 2013.

*Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. GRADE Working Group. BMJ 2008;336:924–6.

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