

## Stillbirth risk factors, causes and evaluation

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### ABSTRACT

Stillbirth impacts 5.73 per 1,000 births in the United States and this rate exceeds that of contemporary high-resource countries.<sup>1,2</sup> Risk factors include both demographic and medical characteristics. There are also numerous pathophysiologic mechanisms that can lead to stillbirth. Unfortunately, these risk factors are fairly common, making stillbirth risk stratification and prevention challenging. This is due in part to a large number of unexplained stillbirths. In a large, multi-center study of stillbirths, approximately 24% of stillbirths remained unexplained following thorough, standardized evaluation.<sup>3</sup> The number of unexplained stillbirths is unquestionably larger outside of a rigorous study protocol, but real-world data are lacking. This large proportion of unexplained stillbirth cases makes achieving further decreases in the stillbirth rate difficult given lack of understanding of underlying causes in this population. Cause of death identification can be improved with adoption of an evidence-based, comprehensive stillbirth evaluation.

### Risk factors

In resource-rich countries, the most common risk factors associated with stillbirth are nulliparity, advanced maternal age, non-Hispanic Black race, obesity, pregestational diabetes, chronic hypertension, tobacco or alcohol use, multiple gestation, male fetal sex, unmarried status, and past adverse obstetric outcomes.

### Social factors

#### Racial disparities and inequities

Substantial racial disparities exist in stillbirth rates in the United States. In 2021, the stillbirth rate ranged from 3.94 per 1000 total births for Asian individuals to 4.85 for non-Hispanic White individuals to 9.89 for non-Hispanic Black individuals.<sup>1</sup> Among those of Hispanic origin, the 2021 U.S. stillbirth rate was 4.82 per 1000 total births.<sup>1</sup> According to a multisite prospective population-based, case-control study conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Stillbirth Collaborative Research Network (SCRN), a higher proportion of stillbirths occurring in non-Hispanic Black patients compared with non-Hispanic White patients were associated with obstetric complications (43.5% vs. 23.7%,  $p < 0.001$ ) and infections (25.2% vs. 7.8%,  $p < 0.001$ ), respectively.<sup>3</sup>

This racial disparity in stillbirth rates persists even among those with

adequate prenatal care and higher educational levels.<sup>4,5</sup> Rather than labelling race as a risk factor for adverse perinatal outcomes, current efforts to reframe the discourse on racial health inequities are ongoing and consider racism as a risk factor instead. Racism includes implicit and explicit bias in healthcare as well as structural racism. Structural racism refers to the totality of ways in which societies perpetuate racial group inequities through mutually reinforcing systems of housing, education, employment, income, benefits, credit, media, healthcare, and criminal justice.<sup>6</sup> Residential racial segregation in the U.S. is suggested as a key determinant of racial health disparities since discriminatory housing policies have resulted in geographic separation by race, resulting in limited access to resources among segregated black communities.<sup>7</sup> A retrospective cohort study using a national database system demonstrated residential areas with low levels of racial segregation were associated with a greater reduction in the odds of stillbirth among Black patients than among White patients and predicted that decreasing racial segregation may prevent several hundreds of stillbirths annually among Black patients in the U.S.<sup>7</sup>

#### Maternal age

Stillbirth risk and maternal age follow a bimodal distribution. Stillbirth rates were highest for those under age 15 (13.14 per 1000 total births) and aged 45 or older (11.36 per 1000 total births).<sup>1</sup> The higher rates at the extremes of age are not entirely understood. In advanced

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maternal age, the increased risk of stillbirth persists even when accounting for medical comorbidities, parity, race/ethnicity, and anomalous fetuses.<sup>8</sup>

#### Marital status, education, and income

Compared to married pregnant patients, those that were unmarried and not cohabitating had an increased risk of stillbirth, with an adjusted odds ratio (aOR) of 1.62 (95% CI 1.15-2.27).<sup>9</sup> Screening for partner relationship may prove to be useful in identifying higher-risk women who would benefit from social support during pregnancy. In terms of educational status, the SCRIN study did not demonstrate an increased stillbirth risk across lower educational groups compared to those with college and beyond.<sup>9</sup> No difference in rates of stillbirth were observed across various insurance statuses or family incomes as well.<sup>9</sup>

#### Substance use in pregnancy

In 2021, the stillbirth rate for U.S. women who smoked during pregnancy (9.62 per 1000 total births) was more than 1.5 times higher than that for women who did not smoke during pregnancy (5.08).<sup>1</sup> There is a clear dose-response effect of smoking during pregnancy on the risk of stillbirth, and quitting smoking between pregnancies may be protective. However, caffeine and alcohol use were not consistently associated with stillbirth.<sup>9,10</sup> Pregnant patients with a substance use disorder had an increased risk of stillbirth with an aOR of 2.08 (95% CI 1.12-3.88).<sup>9</sup>

#### Environment/climate

Emerging evidence suggests that increases in air pollutants and heat exposure related to climate change are associated with adverse pregnancy outcomes, including stillbirth in the U.S.<sup>11</sup> The pathophysiology of increased air pollutants associated with stillbirth outcomes may involve alterations in the oxygen transport, DNA damage, or placental injury. Women with asthma may be particularly susceptible to adverse obstetric outcomes associated with increased air pollutants and heat exposure.<sup>11</sup>

#### Maternal conditions

##### Pregnancy history

Both nulliparity and a history of stillbirth in prior pregnancy independently increase the risk of stillbirth. According to the SCRIN population-based study, pregnancy history is considered to be the strongest risk factor for stillbirth.<sup>9</sup> When compared with multiparous individuals without previous pregnancy losses, there was a progressive increase in stillbirth risk for nulliparas with an aOR of 1.98 (95% CI 1.51-2.60) followed by nulliparas with previous losses at less than 20 weeks' gestation with an aOR 3.13 (95% CI 2.06-4.75), and then multiparas with a previous stillbirth with aOR 5.91 (3.18-11.00).<sup>9</sup> Of note, multiparas with no stillbirth history but with previous miscarriages at < 20 weeks' gestation were not associated with increased risk of stillbirth.<sup>9</sup> Prior history of a small-for-gestational-age infant born before 34 weeks was associated with increased risk of stillbirth with odds ratio of 6.00 (95% CI 3.43-10.49).<sup>10</sup>

##### Maternal obesity

Maternal obesity (defined as pre-pregnancy body mass index, BMI, > 30) is an independent risk factor associated with stillbirth with an aOR of 1.43 (95% CI 1.09-1.88) for BMI 25-30, an aOR of 1.72 (95% CI 1.22-2.43) for BMI 30-34, and aOR of 1.73 (95% CI 1.23-2.45) for BMI  $\geq$  35.<sup>9</sup> Excessive weight gain during pregnancy is also associated with a higher risk of stillbirth among obese and morbidly obese women. The risk of stillbirth related to obesity may increase with advancing gestational age, and increasing placental dysfunction may play a role in the pathophysiology.<sup>12</sup>

**Table 1**

Risk Factors Associated with Stillbirth.

Risk Factor	Estimated rate of stillbirth per 1000 births
All Pregnancies**	5.73
Gestational diabetes on diet**	6-10
Gestational diabetes on insulin**	6-35
Chronic hypertension**	6-25
Preeclampsia without severe features**	9-51
Preeclampsia with severe features**	12-29
Fetal growth restriction**	10-47
Twins**	12.37
Triplets or higher-order**	27.84
Oligohydramnios**	14
Post term pregnancy ( $\geq$ 42 weeks)**	5.54
Previous stillbirth**	9-20
Decreased fetal movement**	13
Systemic lupus erythematosus**	40-150
Renal disease**	15-200
Cholestasis of pregnancy**	12-30
Maternal age < 15 years**	13.14
Maternal age 15-19 years**	7.19
Maternal age 35-39 years**	6.28
Maternal age 40-44 years**	8.52
Maternal age 45 years or greater**	11.36
Black maternal race (non-Hispanic)**	9.89
BMI > 30**	13-18
Smoking**	9.62

\*\* Data adapted from Gregory ECW, Valenzuela CP, Hoyert DL. Fetal Mortality: United States, 2021. Natl Vital Stat Rep. 2023;72(8):1-21. PMID: 37498278.

\*\* Data 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.

#### Comorbid medical conditions

Many maternal medical conditions are associated with increased risk of stillbirth. Pregestational diabetes is a known risk factor for stillbirth with aOR 2.50 (95% CI 1.39-4.48).<sup>9</sup> In the SCRIN study, diabetes during pregnancy was considered to be a possible or probable cause of death in 4.1% of stillbirths.<sup>3</sup> Strict pre-pregnancy glycemic control with a HgbA1c < 7% and euglycemia during pregnancy may reduce the risk of stillbirth.<sup>13</sup> Chronic hypertension is also associated with an increased risk of stillbirth and can increase the risk of stillbirth by 2-4 fold. (Table 1) A recent multicenter randomized trial demonstrated that targeting blood pressures of less than 140/90 in patients with chronic hypertension reduced the incidence of the composite adverse pregnancy outcome (including fetal or neonatal death) without compromising fetal growth.<sup>14</sup>

Many other maternal medical conditions have been associated with stillbirth and include systemic lupus erythematosus, renal disease, poorly controlled thyroid disease, and intrahepatic cholestasis of pregnancy. Sickle cell disease, an autosomal recessive hemoglobinopathy that is characterized by chronic hemolytic anemia and vaso-occlusive complications, is associated with increased risk of stillbirth with relative risk of 3.99 (95% CI 2.63-6.04).<sup>10</sup>

#### Fetal conditions

##### Plurality

The stillbirth rate for twins (12.37 per 1000 total births) was more than twice that for singletons (5.49 per 1000 total births), whereas the rate for triplets or higher-order deliveries (27.84 per 1000 total births) was five times that for singletons.<sup>1</sup> The stillbirth rate among mono-chorionic twin pregnancies is approximately two times higher than dichorionic twin pregnancies; this is due to complications specific to multiple gestation, such as twin-twin transfusion syndrome, as well as increased risks of aneuploidy, congenital anomalies, and growth restriction.<sup>15</sup> The risk of stillbirth increases in all twins with advancing

**Table 2**  
Most Common Probable and Possible Causes of Stillbirth per SCR N Study.

Cause	Percentage*
Obstetric Complications	29.3%
Placental disease	23.6%
Fetal genetic/structural anomalies	13.7%
Infection	12.9%
Umbilical cord abnormalities	10.4%**
Hypertensive disorders	9.2%
Other maternal medical complications	7.8%
Other	3.1%

\* some stillbirths had more than 1 probable cause

\*\* umbilical vein thrombosis was not included in original analysis. Inclusion of umbilical vein thrombosis increases the rate of umbilical cord abnormality-associated stillbirth to 19%

gestational age, and therefore, delivery before the estimated due date is often recommended to prevent late stillbirth.<sup>15</sup>

## Causes

Identifying the likely cause of the fetal death can be challenging, especially considering the non-uniformity of data reporting and multi-factorial processes involved in a stillbirth. The Initial Causes of Fetal Death Evaluation (INCODE) algorithm was developed by the SCR N investigators as a standardized classification system to assign probable and possible causes of stillbirth based on information routinely collected during prenatal care and the clinical evaluation of fetal death.<sup>16</sup>

A condition is considered to be a *probable cause* of stillbirth if it has a high likelihood of directly causing fetal death. If a condition was not a direct cause of the stillbirth, but possibly involved in a pathophysiologic sequence that led to the fetal death, it was considered a *possible cause*. A *present cause* is a condition that is documented but in remission, controlled with medications, or not deemed to be involved in the etiology of fetal death. INCODE acknowledges the uncertainty of assigning a specific cause of stillbirth from many potential causes. For example, diabetes would be considered a probable cause if the fetus had diabetic embryopathy or if the stillbirth occurred during an episode of maternal diabetic ketoacidosis; a possible cause would be if the mother had poor glycemic control and the fetus had abnormal growth; and the diabetic condition is present if the mother had good glycemic control and the fetus had no other abnormalities.<sup>16</sup> For the most part, present conditions are potential risk factors for stillbirth, rather than causes.

The INCODE contains six broad categories as potential causes of fetal death and a final seventh category to list other conditions.<sup>16</sup>

- (1). Maternal medical conditions including diabetes and hypertension.
- (2). Obstetric complications such as fetal maternal hemorrhage, cervical insufficiency, or abruptio placentae.
- (3). Umbilical cord abnormalities.
- (4). Fetal genetic, structural, and karyotype conditions.
- (5). Infection.
- (6). Placental abnormalities.
- (7). Other conditions such as hydrops and early amnion rupture sequence.

Based on the prospective population-based case-control SCR N study, a probable cause of stillbirth was identified in approximately 61% of cases, and a possible or probable cause in 76% of cases.<sup>3</sup> The most common causes were obstetric conditions observed in almost 30% of stillbirth cases, followed by placental abnormalities observed in approximately 24% of cases.<sup>3</sup> (Table 2)

Almost one-fourth of stillbirths in the U.S. are considered potentially preventable, and the most common cause of potentially preventable stillbirths was placental insufficiency as demonstrated by fetal growth

restriction or oligohydramnios, in which adequate antenatal fetal surveillance may reduce the stillbirth risk. Other common causes of potentially preventable stillbirths include maternal medical disorders such as hypertensive conditions, in which optimal medical care would decrease the stillbirth risk.<sup>17</sup>

## Obstetric complications

The category for obstetric complications is the most common broad category of probable and possible causes of stillbirth. This category includes intrapartum fetal death, placental abruption, fetal maternal hemorrhage (FMH), uterine rupture, preterm labor or rupture of membranes, and clinical chorioamnionitis.<sup>3</sup>

Fetal-maternal hemorrhage (FMH) can be considered a cause of fetal death if the hemorrhage exceeds 40% of fetal blood volume.<sup>16</sup> To calculate the FMH blood volume, the following calculations can be performed:<sup>16</sup>

- (1). Total fetal blood volume = 125 mL per kilogram of fetal weight.
- (2). FMH red cell volume = maternal blood volume x maternal hematocrit x fetal red blood cells in maternal sample.
- (3). FMH whole blood volume = (FMH red cell volume) / (total fetal blood volume).

## Placental disease

Placental disease is considered to be the second most common broad category of probable/possible causes, accounting for almost 24% of stillbirths.<sup>3</sup> Placental disease includes circulation abnormalities, uteroplacental insufficiency, and abnormal maturation of the placental disc. Circulation abnormalities would be detected on histopathology as villous parenchymal infarcts or massive fibrin deposition on the maternal interface, thromboemboli on the fetal interface, or massive subchorionic hematoma. When placental pathologic findings occur in association with a maternal or fetal condition (e.g., placental infarcts in association with antiphospholipid syndrome), then the condition itself is considered to be a possible or probable cause of death, rather than the placental anatomic abnormality.<sup>16</sup> Among these various placental diseases, thromboembolism in fetal circulation tends to be the most common cause, accounting for 34.7% within the broad category.<sup>3</sup>

Isolated incidental histologic chorioamnionitis, which involved extensive polymorphonuclear cell invasion of the placental membranes, is considered a *present condition*, as there is insufficient evidence to include this pathologic diagnosis as a probable or possible cause of death. However, histologic funisitis, in which the umbilical cord is also affected by extensive polymorphonuclear cell invasion, can be considered causal for stillbirth.<sup>16</sup>

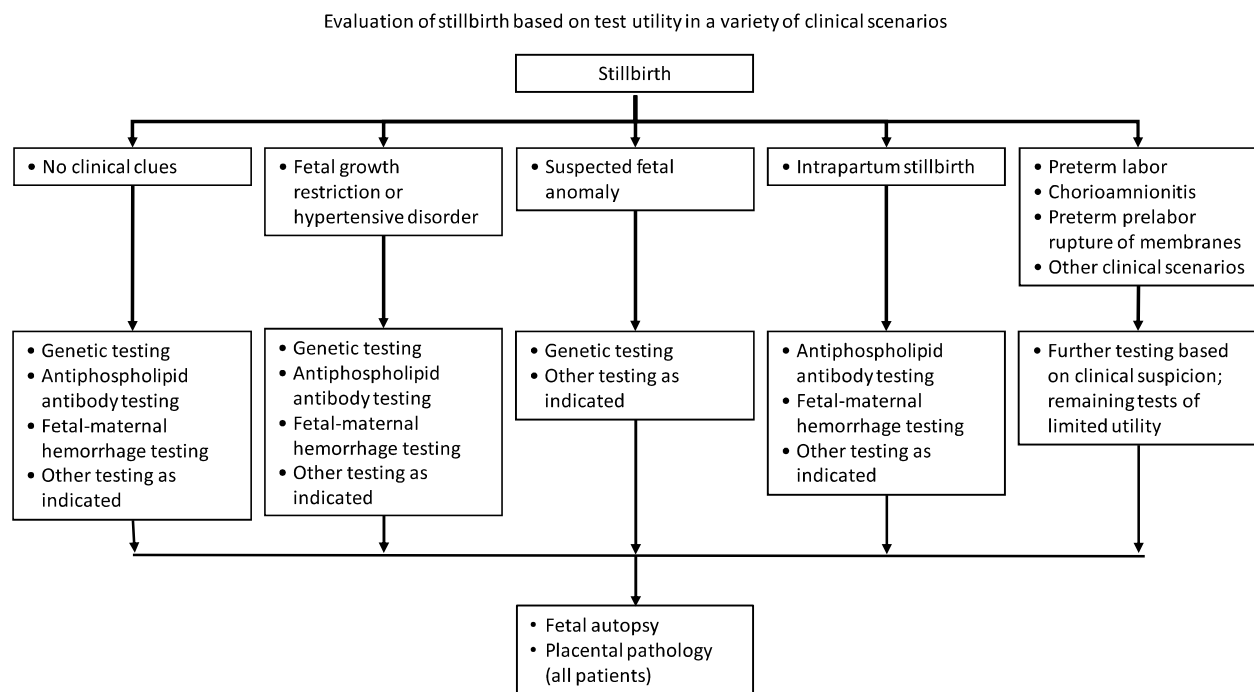
Although small for gestational age (SGA) is commonly associated with stillbirth, it is not often a cause of fetal death and is considered a consequence of other underlying intrinsic conditions that adversely influence fetal well-being and are possible or probable causes of fetal death.<sup>16</sup> Severe fetal growth restriction with estimated fetal weight less than the third percentile were at the greatest risk of stillbirth.

## Fetal genetic or structural anomalies

Fetal genetic or structural anomalies account for approximately 14–18% of stillbirths with aneuploidy being the most common cause within this category.<sup>3,18</sup> Other causes within this category would include non-immune hydrops, urogenital anomaly with anhydramnios, abdominal wall defects, neural tube defects, and other conditions. As molecular technologies become more available for genetic diagnosis following stillbirth, the proportion of cases due to this, and our collective understanding of the pathophysiologic mechanisms, will improve.

## Infection

Infection accounts for approximately 12.9% of possible/probable



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 Apr;129(4):699-706.

Fig. 1. An Algorithm for Stillbirth Evaluation.

causes of stillbirth in well-resourced countries.<sup>3</sup> Infections may result in stillbirth by direct fetal infection, placental dysfunction, severe maternal illness, or triggering spontaneous preterm birth. Within this broad category, fetal infection involving vital organs tends to be the most common sub-category followed by fetal membranes and placental inflammatory disorders.<sup>3</sup>

Placental and fetal infections most commonly result from ascending bacterial infection from the vagina into the space between the maternal decidua and the chorion. Further spread may result in the organisms reaching the amniotic fluid or the fetus. Examples include group B *streptococcus* and *E. coli*. Maternal systemic infections may also spread hematogenously and reach the fetus through the placental villi (villitis). These types of infections typically involve the fetal liver, as the first major fetal organ reached, with relatively less-common organisms such as *Listeria*.

Syphilis, which is uncommon in the U.S., is still responsible for some stillbirths, particularly in endemic areas and in developing countries.<sup>19</sup> Malaria is a cause of stillbirth when a first infection occurs during pregnancy. This also is an extremely common cause of stillbirth in endemic areas in low resource settings.<sup>20</sup>

Viral infection may also cause stillbirth. Parvovirus is usually asymptomatic in adults but may result in stillbirth due to the destruction of erythropoietic tissue leading to severe anemia and hydrops. It also may cause myocarditis and myocardial dysfunction. Cytomegalovirus (CMV) is the most commonly acquired congenital viral infection, with a primary infection rate of 0.4% during pregnancy. A known cause of fetal and placental damage, CMV has been associated with sporadic stillbirths.<sup>21</sup>

COVID-19 in pregnant individuals can result in severe infection resulting in maternal viremia with multi-organ involvement, including the placenta. Increased risk of stillbirth was especially associated with COVID-19 when pregnant individuals were infected during early and mid-pregnancy intervals (before 20 weeks' gestation and between 21-27 weeks' gestation respectively), rather than immediately before delivery or during the third trimester, suggesting the potential vulnerability of

the fetus and placenta to the SARS-CoV-2 infection in early pregnancy.<sup>22</sup> Vaccinations against SARS-CoV-2 not only decreases the severity of COVID-19 syndrome and associated adverse perinatal events, but booster doses during pregnancy may elicit robust immune responses in mothers and enhance transplacental antibody transfer to the newborn.<sup>23</sup>

In cases of stillbirth in mothers with COVID-19, the placental pathology consists of three pathologic lesions, collectively known as SARS-CoV-2 placentitis: 1) increased fibrin deposition reaching the level of massive perivillous fibrin deposition, 2) chronic histiocytic intervillitis, and 3) trophoblast necrosis. This diffuse placental parenchymal destruction leads to malperfusion and placental insufficiency to the point of resulting in fetal death.<sup>24</sup> Asymptomatic or mild cases of SARS-CoV-2 have not been associated with fetal death.<sup>25</sup>

#### Medical conditions

Within maternal medical conditions, hypertensive disorders of pregnancy account for a substantial proportion of possible/probable causes of stillbirth followed by diabetes.<sup>3</sup> Other maternal medical conditions include antiphospholipid syndrome, maternal substance use, intrahepatic cholestasis of pregnancy, and other disorders.

#### Umbilical cord abnormalities

Stillbirth due to umbilical cord abnormality, also referred to as "cord accident," occurs when blood flow through the cord is sufficiently impaired to cause fetal death.<sup>26</sup> Umbilical cord abnormalities can account for 10-19% of all stillbirths and 28% of stillbirths at or beyond 32 weeks' gestation.<sup>3,26</sup> An umbilical cord abnormality is defined by five conditions: 1) cord entrapment (nuchal, body or shoulder cord accompanied by evidence of cord occlusion on histopathologic examination); 2) knots, torsions, or strictures with histopathologic evidence of thrombi or other obstruction; 3) cord prolapse; 4) vasa previa; and 5) compromised fetal microcirculation seen as a histopathologic finding.<sup>26</sup> Since nuchal cords are noted in almost one-fourth of uncomplicated deliveries, nuchal cord alone should not be considered as a cause of stillbirth.<sup>3</sup> Cord entrapment, on the other hand, is nuchal, body, or shoulder cord with

accompanied by evidence of cord occlusion on histopathologic examination. While even multiple nuchal loops are not necessarily associated with stillbirth, cord entrapment is associated with adverse intrapartum events. Similarly, true knots are common incidental findings that result in healthy live births in most cases; so, in the absence of histopathologic confirmation, the simple presence of these umbilical cord abnormalities cannot imply the cause of stillbirth.<sup>26</sup>

Compromised fetal microcirculation on histopathology is evidence of vascular obstruction and can be used to confirm umbilical cord abnormality. Typically, compromised fetal microcirculation without clinical evidence of cord obstruction is considered a *possible cause* of stillbirth while cord obstruction confirmed clinically and on histopathology is considered a *probable cause* of stillbirth.

#### Other

Other causes of stillbirth that cannot neatly fit into the aforementioned broad categories include early amnion rupture, maternal trauma during pregnancy, and red cell isoimmunization.

#### Evaluation

An appropriate evaluation to determine a potential cause of death is one of the most critical components of stillbirth care. Identifying a cause of death helps to inform future pregnancy care and stillbirth recurrence risk. It is also often felt to be an important part of the grieving process, as learning a potential cause can help with emotional closure. Moreover, understanding causes and pathophysiologic pathways to stillbirth is imperative to risk reduction and prevention efforts.

Stillbirth evaluation is a complex process due to the heterogeneous nature of fetal death, the fact that more than one contributing cause can be present and the emotional difficulty that underlies this process. However, a thorough and thoughtful stillbirth evaluation can identify a probable cause of death in over 60% of cases and a possible or probable cause in over 80% of cases.<sup>3</sup> Despite these data, many stillbirth cases remain unexplained. In some instances, this is due to lack of appropriate evaluation. In others, there are underlying factors present that our current technologies cannot yet identify.

Stillbirth evaluation begins with a careful examination of the medical and obstetric history and events in the current pregnancy. Numerous medical conditions increase the risk of stillbirth, providing helpful context by which to evaluate the fetal death. Important conditions of interest include a history of venous thromboembolism, hypertension, diabetes, and autoimmune disease. Similarly, if a patient has an obstetric history notable for prior episodes of placental insufficiency (i.e., fetal growth restriction, oligohydramnios), this is important information that can point to possible underlying causes of death in the current pregnancy. A thorough assessment of the events of the current pregnancy is also critical. Inquiring about any maternal illnesses or trauma, abnormal ultrasound findings, or episodes of preterm labor or bleeding can inform the clinical framework for the rest of the stillbirth evaluation.

An algorithm for evaluation of stillbirth has been recommended by the Society for Maternal-Fetal Medicine (SMFM) and the American College of Obstetrics and Gynecology (ACOG).<sup>27</sup> This algorithm incorporates the expected yield of a diagnostic test and tailors testing recommendations around the clinical scenario in which the stillbirth occurred (Fig. 1). This approach aims to balance the yield of a diagnostic test with cost, which can improve the efficiency of the work-up and reduce wasteful medical spending.

The yield or utility of a diagnostic test to help identify or refute a potential cause of stillbirth has been studied in two large stillbirth cohorts. The first included over 1000 cases and evaluated which tests helped to identify a cause of death. In this study, the authors found that the most useful tests for identifying a cause of death included placental pathology (95.7% of cases), fetal autopsy (72.6% of cases), and genetic testing (29.0% of cases).<sup>28</sup> A similar approach was used in a cohort of 512 stillbirth cases from the U.S. In this multicenter, geographically

diverse group, test utility was evaluated by determining if, after considering the clinical scenario, a test helped to identify or refute a potential cause of death. This work demonstrated that the most useful tests included placental pathology (64.6% of cases), fetal autopsy (42.4% of cases), and genetic testing (11.9% of cases).<sup>29</sup> Additionally, it has been shown that placental pathology and fetal autopsy improve the identification of a potential cause of death when added incrementally to clinical and lab information.<sup>30</sup> Given these data, SMFM and ACOG recommends that placental pathology and fetal autopsy be conducted in all stillbirth cases. The remaining tests were useful in only a smaller subset of patients. We will review these elements of the stillbirth evaluation here.

#### Placental pathology

Abnormalities in placental form or function are implicated in many stillbirth cases, with ranges reported from 23–65%.<sup>3,31–33</sup> The relative contribution of placental causes of death depends in part on the stillbirth cause of death classification system used.<sup>34</sup> Regardless, pathologic review of the placenta, umbilical cord, and fetal membranes performed by a perinatal pathologist has been demonstrated in multiple studies to be the single most useful diagnostic test in stillbirth evaluation.<sup>28,29</sup> This exam generally includes an assessment of placental weight compared to normative values for gestational age. A gross evaluation of the placental appearance can reveal important findings including evidence of abruption, umbilical cord thrombosis, and velamentous cord insertion. Microscopic evaluation is a critical tool for evaluating the presence of infection, inflammation, and disordered development.

Evaluation of the umbilical cord is an important component of the placental exam. The term “cord accident” refers to a condition in which a disruption in blood flow through the umbilical cord occurs to the degree that a fetal death occurs.<sup>35,36</sup> Cord occlusion can occur in various settings and can range from acute or chronic, as well as intermittent or persistent. Our tools for antenatal detection of this phenomenon antenatally are lacking, and it remains a controversial and frustrating clinical problem. Cord abnormalities are reported in 2–30% of stillbirth cases, and this wide range is attributed, in part, to varying rigor with which this cause of death is assigned.<sup>3,37</sup> Umbilical cord tangling or knots must be interpreted with caution as cord entanglement occurs in approximately 25% of normal pregnancies. Additional evidence of cord compromise through histopathologic exam is necessary before arriving at cord accident as a cause of death. Pathologic features consistent with a cord-mediated cause of death include vascular ectasia and thrombosis in the umbilical cord, chorionic plate, and stem villi, as well as a regional distribution of avascular villi or villous stromal karyorrhexis.<sup>36</sup> Additionally, fetal autopsy can provide helpful corroborating evidence of significant cord occlusion through physical findings of cord compression and hypoxia.

#### Fetal autopsy

Fetal autopsy is the second most useful component of stillbirth evaluation.<sup>28,29</sup> However, it remains underutilized due to various factors. An assessment of U.S. fetal death certificate data demonstrated that only 20% of stillbirths have a fetal autopsy performed.<sup>38</sup> Many factors are involved in the completion of fetal autopsy. To begin, it is performed by perinatal pathologists, who often work only in large, tertiary care settings. This results in an increased logistical and likely financial burden for families who live in more rural locations. Next, fetal autopsy can be a difficult topic to discuss from an emotional perspective for both providers and patients. The decision to obtain an autopsy can be influenced by the nature of provider counseling and personal and social beliefs.<sup>39</sup> Some patients find the invasive nature of fetal autopsy to be prohibitive, and less invasive techniques are being developed. This includes external only examination, x-rays, limited biopsies, and MRI.<sup>31,40,41</sup> Currently, a complete fetal autopsy remains the most informative of these options, and given the high yield of the exam, it is

imperative that providers feel comfortable and knowledgeable in discussing this with patients.

Despite its underutilization, fetal autopsy is recognized as one of the most useful components of the stillbirth evaluation. It can identify gross morphologic anomalies that are not readily assessed by way of imaging. The autopsy is particularly valuable for its ability to detect more subtle findings that can inform possible causes of stillbirth, such as infection, anemia, hypoxia, and metabolic abnormalities.<sup>42</sup> These findings can identify a cause of death that may or may not have been suspected clinically or rule out previously suspected causes.

#### Genetic testing

Genetic testing can provide important information regarding potential causes of death in many cases of stillbirth and should be offered in most circumstances. Historically, karyotype was performed as the initial test of choice for genetic evaluation following stillbirth, with abnormalities detected in 6-13% of cases.<sup>43,44</sup> However, this test was limited by the need to culture and grow cells, which is not always feasible in this circumstance and can lead to test failure. Karyotype is best performed on cells obtained from amniotic fluid, a placental sample from below the cord insertion including the chorionic plate, an umbilical cord segment or fetal tissue (costochondral, patellar). Amniocytes have the highest success rate, and as such, an amniocentesis should be performed prior to delivery if karyotype is desired.<sup>45</sup>

Given the limitations of karyotyping described above, microarray has become the recommended genetic evaluation for stillbirth.<sup>27</sup> Microarray does not require live cells and can detect deletions or duplications as small as 50 kb termed copy number variants. A study of genetic testing in over 500 stillbirth cases demonstrated that microarray increases the diagnostic yield above that of karyotype with a result in 87.4% of cases tested as compared to 70.5%.<sup>46</sup> This resulted in improved detection of genetic abnormalities that may have been in the pathophysiologic pathway to fetal death, increasing from 5.8% to 8.3% of cases in a cohort of 532 stillbirths.<sup>46</sup> Limitations of microarray include inability to detect balanced genetic changes that do not result in a net gain or loss of genetic material, as well low level mosaicism. Lastly, microarray testing can be costly, and the most cost-effective testing option should be explored with patients when considering genetic testing.

Whole exome and whole genome sequencing are emerging genetic testing strategies that can detect single nucleotide changes and small duplications and deletions of genetic material, representing the most granular genetic testing available. Whole exome sequencing was performed in 246 stillbirth cases without a clearly defined cause of death and identified a probable molecular diagnosis in 8.5% of cases.<sup>18</sup> This increased the proportion of stillbirth cases attributed to genetic causes to 18% in a cohort of over 500 stillbirth cases with thorough evaluation. Whole genome and exome sequencing are not currently widely available and are often cost-prohibitive. However, they are being used in select circumstances and in study protocols and may become the test of choice over time, given the improved detection rate.

#### Antiphospholipid syndrome testing

Antiphospholipid syndrome (APS) is a rare autoimmune disorder diagnosed by a combination of clinical and laboratory criteria. The clinical criteria include arterial, venous, or microvascular thrombosis, adverse pregnancy outcomes, or other non-thrombotic manifestations in those with persistently positive lab testing. The adverse pregnancy outcomes associated with APS include three or more consecutive pregnancy losses at less than or equal to 15 weeks, fetal death at 16 weeks or greater, and preeclampsia with severe features or placental insufficiency prior to 34 weeks. Laboratory assessment includes lupus anticoagulant, anti  $\beta$ 2-glycoprotein-I IgG/IgM, and anticardiolipin IgG/IgM with elevated values greater than the 99th percentile on two occasions 12 weeks apart.<sup>47</sup>

In the Stillbirth Collaborative Research Network (SCRN) study, 582

stillbirth cases and 1547 live birth cases underwent cardiolipin IgG testing. Those that were positive had an OR of 3.43 (95% CI 1.79 – 6.60) for stillbirth as compared to those that tested negative. In further analysis, excluding cases with fetal anomalies, genetic abnormalities, or obstetric complications increased the OR for stillbirth to 5.30 (95% CI 2.39 – 11.76) in those with cardiolipin antibodies.<sup>48</sup>

#### Fetal maternal hemorrhage testing

Fetal to maternal hemorrhage (FMH) is implicated in the pathophysiologic process leading to fetal death in 1-13% of stillbirths.<sup>49,50</sup> FMH of greater than 40% of fetal blood volume before delivery is considered sufficient to cause stillbirth.<sup>16</sup> The results of FMH testing must be interpreted with caution, as a small number of fetal cells may be present in the maternal circulation in uncomplicated pregnancies as well. Both the Kleihauer-Betke and flow cytometry are used in determination of FMH and are likely equivalent given the large volume needed for it to be considered a clinically significant finding.

Testing for FMH is recommended performed ideally prior to delivery to avoid confounding fetal-maternal blood transfer that may occur in that process. FMH testing was positive in 12% of stillbirth cases in a large 1025-patient cohort, but was deemed the likely cause of death in only 1.3% of cases.<sup>28</sup>

#### Infection

Infection is involved in approximately 10% of stillbirths in high-income countries and a considerably higher proportion in low-resource settings.<sup>3,51</sup>

Given the relative infrequency of infection with a specific pathogen, routine screening for these infections following fetal death is likely of low utility and not cost-effective. Additionally, a positive screening test in isolation, without correlating clinical evidence of significant infection in the patient's presentation or on pathologic exam, provides little information regarding a potential cause of fetal death. Placental and fetal pathology often demonstrate characteristic findings or microscopically visible organisms indicating specific infections such as cytomegalovirus, parvovirus, or syphilis. Even in the absence of this, acute and chronic inflammation in the fetus and placenta can provide evidence of infection.

Of the 512 SCRN stillbirth cases, 66 (12.9%) had a possible or probable infection cause of death, and infection test utility was assessed in this group. The most common pathogens included *E. coli*, Group B streptococcus, enterococcus, and cytomegalovirus. Convincing evidence of significant pathologic infection was obtained from the results of fetal autopsy, placental pathology, and the clinical history with infection testing serving in a confirmatory fashion. As such, routine screening was not recommended in cases without other findings suggestive of infection.<sup>52</sup>

#### Other conditions

Additional testing included in the recent guidance from SMFM and ACOG for selected cases includes indirect Coombs, glucose screening, and toxicology screening.<sup>27</sup> These tests have not been demonstrated to be of high utility in determining a cause of death as a general screening test.<sup>29</sup> Most maternal medical comorbidities will likely be known when significant enough to lead to stillbirth, and testing should be initiated when clinically suspected. For example, in the setting of a significantly large for gestational age fetus, testing for diabetes is reasonable. Likewise, if there is evidence suggestive of fetal anemia, such as hydrops, an antibody screen and parvovirus testing should be performed. Intrahepatic cholestasis of pregnancy is also associated with stillbirth, and testing should be considered in the setting of maternal pruritis or elevated liver enzymes.<sup>53</sup>

Some illicit drugs are associated with an increased risk for stillbirth, but as most infants exposed to these substances are live-born, routine screening is not recommended.<sup>51</sup> Previously, several inherited thrombophilias had been thought to be associated with stillbirth, but more

**Table 3**  
Components of the Stillbirth Evaluation.

Key Component	Description
Fetal Autopsy	If patient declines autopsy, alternatives include MRI, photographs, X-ray, ultrasound and selective tissue sampling of tissues
Placental Evaluation	Targeted viral and bacterial infection testing based on pathologic findings
Fetal Karyotype/ Microarray	Greatest yield with amniocentesis prior to delivery. Alternatively, umbilical cord sample proximal to placenta can be used.
Maternal evaluation	Corresponding laboratory studies
• Fetal-maternal hemorrhage screen	• Kleihauer-Betke test or flow cytometry
• Antiphospholipid antibody syndrome	• lupus anticoagulant, anticardiolipin antibodies, and $\beta_2$ glycoprotein antibodies testing
• Syphilis testing	• Rapid plasma regain (RPR)
Selected Cases	
• Glucose and diabetes screening	• Glucose and diabetes screening
• Drug use is suspected or cases of placental abruption	• Drug use is suspected or cases of placental abruption
• Consider if not previously performed	• Consider if not previously performed
• Serology, culture or nucleic testing in cases suspected based on history, placental evaluation, autopsy.	• Serology, culture or nucleic testing in cases suspected based on history, placental evaluation, autopsy.

recent rigorous evaluation has not demonstrated this.<sup>54</sup> Additionally, thrombophilias have not been correlated with significant pathologic vascular placental lesions in stillbirth cases.<sup>55</sup> As such, routine testing for inherited thrombophilias is not recommended. Table 3 is a summary of the stillbirth evaluation recommended.

## Disclosure

Drs. Gandhi and Page have no relevant disclosures.

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