Published in final edited form as:
Am J Obstet Gynecol. 2007 May ; 196(5): 433–444. doi:10.1016/j.ajog.2006.11.041.

WORK-UP OF STILLBIRTH: A REVIEW OF THE EVIDENCE

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Abstract

Despite improvements in antenatal and intrapartum care, stillbirth, defined as in utero fetal death at 20 weeks of gestation or greater, remains an important, largely unstudied, and poignant problem in obstetrics. Over 26,000 stillbirths were reported in the US in 2001. Although several conditions have been linked to stillbirth, it is difficult to define the precise etiology in many cases. This paper reviews known and suspected causes of stillbirth including genetic abnormalities, infection, fetal-maternal hemorrhage, and a variety of medical conditions in the mother. The proportion of stillbirths that have a diagnostic explanation is higher in centers that conduct a defined and systematic evaluation. Recommended diagnostic tests for stillbirth are discussed. The on-going work of the NICHD Stillbirth Collaborative Research Network, a consortium of 5 academic centers in the United States that are studying the scope and causes of stillbirth, is presented.

Keywords

Stillbirth; etiologies; work-up

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INTRODUCTION

Few obstetric complications are as emotionally devastating for patients and clinicians as stillbirth, defined as *in utero* fetal death at 20 weeks of gestation or greater. In the United States in 2001, 26,359 stillbirths were reported to the National Center of Health Statistics. This is comparable in magnitude to the 27,568 infant deaths that were registered in the same year. The stillbirth rate declined by only about 17 percent between 1985 and 2001, from 7.8 to 6.5 deaths/1000 births, compared with a 35% decline in infant mortality over that time period. If those rates of decline continue unchanged, the number of stillbirths in the United States should exceed the number of infant deaths by the year 2007. Approximately half of stillbirths occur prior to 28 weeks of gestation and about 20 percent are at or near term.

A persistent and significant racial disparity exits in the rates of stillbirth. In 2001, the rate was of 5.5/1000 live births plus stillbirths among white mothers and 12.1/1000 among black or African American mothers. According to an analysis of U.S. vital statistics between 1995 and 1998, the increased risk of black, compared with white stillbirths is greatest among singleton stillbirths[1]. Of note, one of the US national health objectives for 2010 is to reduce fetal deaths ≥20 weeks' gestation to 4.1/1000 LB, as well as to reduce fetal deaths for all racial and ethnic groups.

Despite the magnitude of the problem, relatively little attention has been focused on stillbirth during the past decades. Accordingly, many clinicians are uncertain as to the optimal evaluation of stillborn infants. In this manuscript, we will review generally accepted causes of stillbirth and current evidence for recommendations for the evaluation of stillborn infants.

CLASSIFICATION OF STILLBIRTH

In many cases it is difficult to be certain of the etiology of stillbirth. First, many cases are "unexplained," despite intensive investigation of potential causes. Second, more than one condition may contribute to stillbirth in an individual case. For example, infection could occur in a fetus with trisomy 18. It may not be possible to precisely determine which disorder was directly responsible for the loss. Indeed, it is likely that some cases of stillbirth are due to contributions from multiple factors. Finally, conditions may be associated with stillbirth without directly causing them. A potential example would be finding that a normotensive woman delivering a nine pound stillborn infant at 39 weeks of gestation has a heritable thrombophilia (e.g. heterozygote for the factor V Leiden mutation). Although this condition has been associated with stillbirth in retrospective studies, it is not clear that the thrombophilia caused the fetal death in this case.

These concerns have led to the development of several classification systems for causes of stillbirth. No single classification system is universally accepted and each has strengths and weaknesses. There are two additional sources of confusion when considering these schemes. First, the definition of stillbirth varies among investigators, countries, health organizations, and classification schemes. Second, many systems are designed to include both stillbirths and neonatal deaths under the blanket heading of perinatal mortality. It is likely that stillbirth over various gestational ages, as well as stillbirth and neonatal death, are due to overlapping but distinct sets of disease states. Thus, etiologies for neonatal death may not be relevant to stillbirth at 20 weeks of gestation.

The first attempt to classify causes of perinatal death was published by Baird using the Aberdeen clinicopathological classification [2]. This scheme was entirely based on available clinical information. In 1958, Butler and Bonham developed a novel classification based on the British perinatal mortality survey that included the results of postmortem examinations [3]. In 1977, Naeye added placental findings in his proposal of a new classification [4]. In 1980,

Wigglesworth introduced the nine category classification system that is currently most commonly used in reporting perinatal mortality rates **(**Table I), [5,6].

There have been several other attempts to classify causes of stillbirth [7–9]. All of these classifications use the traditional definition of perinatal death and include neonatal death, as well as stillbirth. However, since neonatal morbidity and mortality may have different etiological and pathogenetic mechanisms than stillbirth, they need to be separately addressed. Gardosi et al, recently proposed a new classification scheme in which neonatal deaths are excluded [10]. Although this classification mentions the coding of primary and secondary "causes" of stillbirth, the goal is to identify the relevant conditions present at the time of death *in utero*. It is a hierarchical classification where the hierarchy starts from the conditions directly affecting the fetus and moves "outward" in anatomical groups **(**Table II). The authors demonstrated a significant decrease of unclassified stillbirth when compared to Wigglesworth's classification. These authors emphasize the important contribution of fetal growth restriction; with approximately 50% of stillbirths associated with fetal growth restriction[10].

Another point that deserves emphasis is the definition and establishment of conditions that cause inevitable death of a fetus. General definition of "cause of death" is injury or disease responsible for a death. Frøen defines cause of death in stillbirth as "an event or condition of sufficient severity, magnitude and duration for death to be expected in a majority of such cases in a continued pregnancy in the clinical setting where it was observed" [11]. In forensic medicine this definition is supplemented by the manner of death which adds more information about the event. Manner of death defines the circumstances under which a death occurs, such as suicide or accident. When we examine the "causes of death" in numerous classifications or databases regarding stillbirth, it becomes obvious that except for a handful of disorders, most of these conditions do not fulfill the criteria for causing unavoidable death of a fetus. In addition to obvious events like maternal death or abruptio placenta totalis, there are few conditions that cause inevitable death. Table III is a partial list of conditions that are proven to cause fetal demise. Most conditions that have been linked to stillbirth can be classified as associations, rather than unequivocal causes.

KNOWN OR SUSPECTED CAUSES OF STILLBIRTH

Genetics

A substantial proportion of stillbirths may be attributed to genetic causes. The most straightforward genetic etiology for stillbirth is karyotypic abnormalities. These are present in approximately 6 – 12% of stillbirths [12,13]. However, in many cases of stillbirth it is not possible to successfully culture cells to determine karyotype. Thus, the rate of chromosomal abnormalities in cases of stillbirth is likely underestimated. The proportion of chromosomal abnormalities is higher in stillbirths with structural malformations (compared to apparently normal fetuses). The most common specific abnormalities are similar to those noted in live-born infants and include monosomy X (23%), trisomy 21 (23%), trisomy 18 (21%), and trisomy 13 (8%).

Many stillborn fetuses with normal karyotypes have genetic abnormalities. Indeed, 25 – 35% of stillborn infants undergoing autopsy have intrinsic abnormalities [12,14]. These include single malformations (40%), multiple malformations (40%) and deformations or dysplasia (20%) [12]. Approximately 25% of stillborn fetuses with intrinsic abnormalities have an abnormal karyotype. Nonetheless, it is likely that many, if not most, of the remaining 75% have genetic abnormalities that are not identified by conventional cytogenetic analysis. This is especially true for stillbirths with multiple malformations.

Early fetal death may be associated with single gene mutations. Indeed, in transgenic mice, several single gene mutations appear to cause embryonic death. These mutations lead to fetal death at mid-gestation due to abnormal placental growth, development, or angiogenesis. It is likely that human homologues account for some cases of pregnancy loss in women. Some autosomal recessive disorders including glycogen storage diseases and hemoglobinopathies have been reported as the cause of stillbirth [12]. X-linked disorders may also be lethal in male fetuses. Finally, although it is controversial, heritable thrombophilias have been associated with stillbirth (see below) and may be considered a “genetic” cause.

A variety of other genetic abnormalities that are not identified by traditional cytogenetic analysis likely contribute to stillbirth. For example, chromosomal microdeletions that are undetectable by conventional karyotype are associated with otherwise unexplained mental retardation[15]. Also, genetic abnormalities of the placenta (even in the setting of normal fetal karyotype) may contribute to stillbirth. This phenomenon of abnormal chromosomes in some or all placental tissue (but not the fetus) is referred to as confined placental mosaicism. Confined placental mosaicism has been associated with fetal growth impairment and stillbirth [16].

Infection

Stillbirths have been associated with bacterial, protozoal, and viral infections. In developed countries, 10–25% of all stillbirths appear to be caused by a maternal/fetal infection. By contrast, bacterial infection is more prevalent among stillbirths in developing countries[17, 18] Infection may cause stillbirth by a number of mechanisms including direct infection, placental damage and severe maternal illness. The earlier (in gestation) the stillbirth, the more likely it will be associated with infection. In one study, 19% of fetal deaths less than 28 weeks were associated with an infection, while only 2% of term stillbirths were infection-related [19].

In developed countries, ascending bacterial infection, both prior to and after membrane rupture, with organisms such as E. coli, group B streptococci, and Ureaplasma urealyticum is the most common infectious cause of stillbirth [17,18]. In endemic areas, syphilis may cause a large proportion of stillbirths. Malaria may be an important cause of stillbirth in women infected for the first time in pregnancy. Toxoplasma gondii, leptospirosis, Listeria monocytogenes and the organisms which cause leptospirosis, Q fever and Lyme disease have all been implicated as etiologic for stillbirth [18].

The proportion of stillbirths due to viral infection is uncertain, partly due to a lack of a systematic approach to the detection of viral infection in stillborn infants. Many viruses are difficult to culture, and a positive viral serologic result or identification of viral DNA or RNA in fetal/placental tissue does not prove causation. Infection is more clearly associated with early stillbirth (20 weeks) than with late stillbirth (after 28 weeks). The increasing use of molecular diagnostic technology (DNA and RNA PCR) should increase our ability to accurately diagnose viral infections [18].

Parvovirus B-19 appears to have the strongest association with stillbirth. A Swedish survey identified B-19 PCR positive tissues in 8% of stillbirths.[20] In the United States, less than 1% of all stillbirths are reported to be due to parvovirus infection [18]. However, the proportion of stillbirth due to parvovirus may be underestimated due to a lack of systematic testing. Conversely, the Swedish study may overestimate the proportion since a positive PCR result does not prove causality of fetal death. The most common clinical presentation of parvovirus infection in children is erythema infectiosum, or fifth disease, a common childhood exanthem (“slapped cheek” rash). Parvovirus B19 crosses the placenta, infecting fetal erythropoetic tissue, leading to severe fetal anemia. Severe fetal anemia can, in rare cases, result in fetal hydrops, a potential mechanism for fetal death [21]. Parvovirus B19 may also lead to fetal

death by directly attacking fetal cardiac tissue resulting in myocardial damage. It is noteworthy that most pregnancies complicated by acute parvovirus infection do not result in stillbirth [22]. The risk of stillbirth is greater for parvovirus infection occurring prior to 20 weeks gestation[22].

Enteroviruses, including Coxsackie A & B, echoviruses and other enteroviruses, are also associated with stillbirth[23]. Coxsackie viruses can cross the placenta and lead to villous necrosis, inflammatory cell infiltration, calcific pancarditis and hydrops. Echoviruses have been related to stillbirth through severe maternal illness [18].

Cytomegalovirus (CMV), a member of the herpesvirus family, is the most common congenital viral infection. In the United States, about 1% of pregnant women acquire primary CMV during pregnancy. The highest rate of transmission to the fetus, and the most severe consequences, occur with primary maternal infection. CMV has been clearly associated with placental damage leading to intrauterine fetal growth retardation, but an association with stillbirth remains controversial [17,18]. Many vaccine-preventable, childhood viral illnesses (chickenpox, rubella, measles, and mumps) have been implicated in stillbirths in association with a maternal infection. In countries practicing routine vaccination against these viruses, stillbirth is rarely due to these preventable infections.

Fetal maternal hemorrhage

Fetal-maternal hemorrhage has been associated with 3 – 14% of all stillbirths [24–26]. Thus, it accounts for a meaningful proportion of stillbirths. Significant fetal-maternal hemorrhage can be detected in patients undergoing obstetric procedures such as external cephalic version and cesarean section. In addition, hemorrhage can occur with placental abruption and/or abdominal trauma during pregnancy [27]. A reliable test for identification and quantification of fetal-maternal hemorrhage should be performed before the induction of labor. Ideally, evidence of hypoxia and anemia should be confirmed by autopsy before attributing stillbirth to fetal hemorrhage, since small amounts of fetal cells can be detected in maternal blood in uncomplicated pregnancies.

Maternal Characteristics

Prepregnancy obesity, older maternal age and stress are associated with increased stillbirth rates. The underlying mechanisms of action are unknown; however, with obesity and delayed childbearing both on the rise, their importance as potential causes of stillbirth deserves greater attention.[28] Women whose only risk factor is being overweight have about a two-fold increased risk of stillbirth.[29] Likewise, compared with women <35 years of age, the stillbirth rate is increased two-fold for women 35–39 years of age, and 3- to 4-fold for women aged forty or older.[30] While some age-associated risk is due to higher rates of maternal complications, in uncomplicated pregnancies there may be a 50 percent increased risk associated only with maternal age ≥ 35.[31] For older women, stillbirth risk rises more rapidly as gestational age increases beyond 37 weeks. The association between maternal stress and stillbirth is far less well established. Stress may occur as a result of a major life event (such as loss of a child), or through accumulated pressures associated with an ongoing stressful lifestyle (such as poverty) [32], or through unexplained health changes related to adverse childhood experiences.[33]

Maternal Disease

Diabetes—Women with pre-gestational (type I and type II) diabetes mellitus (DM) have an increased risk of second and third trimester stillbirth compared to women without diabetes. Even with modern obstetric care and diabetes management, stillbirth rates in women with type II DM have been reported to be 2.5-fold higher than non-diabetic women [34]. On a population-basis, women with gestational diabetes (GDM) have similar stillbirth rates as a normal

population. However, some women with "GDM" diagnosed during pregnancy actually entered the pregnancy with undiagnosed type II DM, and have the same risk of fetal loss as women with type II DM. Thus, when there is clinical evidence that a woman with GDM may have undiagnosed type II DM, she should be considered to be at increased risk of stillbirth. Examples of women who may have undiagnosed type II DM include those with high fasting glucose values, random or postprandial glucose values >200 mg/dl, history of GDM in prior pregnancies (particularly when no glucose testing was done in the interval between pregnancies), or diagnosis of GDM early in pregnancy.

The factors that account for the increased risk of late pregnancy fetal loss in diabetic women are not fully understood. Although an increased likelihood of fetal anomalies contributes to the increased risk, the stillbirth rate for non-anomalous fetuses is also higher in diabetic women than in non-diabetics. Co-morbid conditions, such as obesity and hypertension, are also more common in women with DM. Fetal growth abnormalities, both growth restriction and excessive growth, are increased in women with DM, and both increase the risk of stillbirth. The link between excessive fetal growth and stillbirth likely involves maternal hyperglycemia leading to fetal hyperglycemia, which in turn triggers excess fetal insulin production to keep fetal plasma glucose levels in the physiologic range. In the fetus, insulin spurs fetal growth, which may result in metabolic acidosis if excessive, and if the placental oxygen supply is insufficient. The endpoint of this process may be a stillbirth.

The exact glycemic threshold that places a diabetic pregnancy at increased risk for stillbirth is not well characterized. However, it has been shown that identifying and treating diabetes lowers the stillbirth rate in these women [35]. Guidelines for the identification and treatment of diabetes are detailed elsewhere.

Antiphospholipid Syndrome—Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the presence of specified levels of antiphospholipid antibodies and one or more clinical features, including pregnancy loss, thrombosis, or autoimmune thrombocytopenia. The two best-characterized antiphospholipid antibodies are lupus anticoagulant and anticardiolipin antibodies. APS is identified as the cause of pregnancy loss in 5 – 10% of women with recurrent miscarriage, although a smaller proportion of women with sporadic stillbirth. The presence of antiphospholipid antibodies also has been associated with fetal death in prospective cohort studies [36,37], strengthening the evidence for an association between this condition and stillbirth. The mechanism of pregnancy loss remains uncertain but probably includes inflammation, thrombosis, and infarction in the placenta. Treatment with thromboprophylactic doses of heparin (7,500 Units twice daily) and low dose aspirin improves obstetric outcome in women with APS. Even treated pregnancies require close surveillance for the development of placental insufficiency.[38]

Other medical disorders—Many other maternal diseases have been linked to stillbirth, including thyroid disease, cardiovascular disease, asthma, kidney disease, and systemic lupus erythematosus.[39] In most cases, this only occurs in the setting of clinical disease and the majority of women with these conditions have normal pregnancy outcomes. Although of research interest, subclinical disease (e.g. thyroid disease or diabetes) has not been convincingly proven as a cause of stillbirth.

Heritable Thrombophilias—The histologic findings of placental infarction, necrosis, and vascular thrombosis seen in some cases of pregnancy loss associated with antiphospholipid antibodies have led to the hypothesis that thrombosis in the uteroplacental circulation may lead to placental infarction and fetal death. In turn, these observations have raised the question as to whether other thrombophilic defects predispose to stillbirth. Several case series and retrospective studies reported an association between heterozygosity for the factor V Leiden

mutation (associated with abnormal factor V resistance to the anticoagulant effects of protein C), heterozygosity for the G20210A mutation in the promoter of the prothrombin gene, and deficiencies of the anticoagulant proteins antithrombin III, protein C, and protein S, and fetal death [40]. Placental infarction was noted in many of these cases. Although more controversial, stillbirth also has been linked to other hypercoagulable states such as hyperhomocysteinemia and deficiencies in levels of activated factor XII.

In most studies, thrombophilias were more strongly associated with losses after 10 weeks of gestation as opposed to anembryonic or embryonic losses. A recent meta-analysis indicated an odds ratio of 2 for "early" (< 13 weeks of gestation) and 7.8 for "late" (19 weeks of gestation) recurrent pregnancy loss for women with the factor V Leiden mutation, and an odds ratio of 2.6 for "early" recurrent fetal loss in those with the prothrombin gene mutation [41]; and an odds ratio of 3.5 for "early" recurrent fetal loss in those with Protein S deficiency. Methylenetetrahydrofolate mutation (homozygosity), protein C deficiency and antithrombin III deficiency were not associated with pregnancy loss in the meta-analysis [41].

It is noteworthy that many heritable thrombophilias are common in normal individuals without a history of thrombosis or pregnancy loss [40]. Thus, although most retrospective studies link thrombophilias to pregnancy loss, most individuals with thrombophilias have uncomplicated pregnancies. Indeed, two large prospective cohort studies indicated no association between the factor V Leiden mutation and heritable thrombophilias and either pregnancy loss or obstetric complications characterized by placental insufficiency [42,43]. The lack of an association between thrombophilias and pregnancy loss in these prospective cohorts raises questions about the validity or strength of an association between thrombophilia and stillbirth. Indeed, thrombophilia is unlikely to cause pregnancy loss in most cases and individuals with thrombophilias but no prior obstetric complications should be reassured.

Exposures Associated With Stillbirth

It is usually difficult to conclusively prove that a stillbirth is due to an external exposure. Nonetheless, a variety of exposures have been implicated as a potential cause of stillbirth. Cigarette smoking is the most common identifiable preventable cause of stillbirth [44]. The odds ratio for stillbirth for a woman who smokes is 1.6 (95% CI: 1.2 – 2.3) [45]. Smoking causes decreased fetal growth and tissue oxygenation as a result of elevated carboxyhemoglobin levels and increased placental vascular resistance. Smoking is also associated with increased risks of placenta previa and placental abruption [46,47]. Women who stop smoking in the first trimester have stillbirth rates equivalent to women who never smoked [48].

Many reports of outcomes in pregnancies complicated by maternal recreational drug use have been criticized because of the confounding effects of maternal multi-drug use and/or maternal underreporting of exposure frequency or variation. Nonetheless, several clear trends have emerged. Cocaine use during pregnancy is associated with a six-fold increased risk of stillbirth, primarily as a result of fetal growth restriction and/or abruption [49]. From national statistics, the use of marijuana during pregnancy has been estimated between 2.9 and 10% [50]. Nonetheless, marijuana use during pregnancy has not been associated with an increased risk of stillbirth [51]. Despite widespread reports linking methamphetamine use during pregnancy with preterm birth and growth restriction, evidence confirming its association with an increased risk of stillbirth remains lacking.

Alcohol consumption in pregnancy has been linked to an increased risk of stillbirth in some reports [52,53], but not in others [54]. Data from Scandinavia suggest relative increases in stillbirth rates from 1.37/1000 births in women who consume < 1 drink per week to 8.83/1000 births in women who consume ≥ 5 drinks/week. When adjusted for smoking habits, caffeine

intake, pre-pregnancy BMI, marital status, occupational status, education, parity and fetal gender, the stillbirth relative risk for women consuming ≥ 5 drinks/week was 2.96 (95% confidence interval = 1.37 – 6.41) [55]. On the other hand, some studies actually report a modest protective effect of small amounts of alcohol consumption during pregnancy on both stillbirth and fetal growth restriction rates [56].

Pastore and associates have demonstrated an association between pesticide exposure and stillbirth [57]. Residential exposure is associated with stillbirth but not with an increased risk of anomalies whereas occupational exposure is associated with an increased risk of stillbirth associated with birth defects.

In the third trimester an increased risk of stillbirth is reported only with maternal radiation doses above 1000 mGy (100 rads) (CDC). However, an intriguing report suggests that a paternal workplace exposure to ionizing radiation may increase the risk of stillbirth [58]. The risk of stillbirth increased by 24% for each 100 millisieverts (mSv) of radiation that a man had been exposed to in his lifetime; it rose even further if the infant had a congenital anomaly, particularly a neural-tube defect.

Pastore and associates have investigated the relationship between medication exposure and stillbirth. Exposure to pain medications is associated with an increased risk of stillbirth whereas exposure to aspirin is not [57]. Of interest, exposure to fertility drugs was associated with a stillbirth relative risk of 1.8 [57]. Of course, this observation illustrates the difficulty in attributing stillbirth to exposures since women undergoing fertility treatments have many confounding variables that may account for the increased risk of stillbirth.

The majority of data regarding exposures and stillbirth are derived from retrospective studies that are subject to considerable recall bias. Most studies also suffer from numerous potential confounding variables that may not be accounted for by statistical analysis. In the absence of prospective studies, the associations between exposures and stillbirth should be viewed with caution.

Stillbirth and Multiple Gestation

Multiple pregnancies constitute about 3% of all births but 10% of all stillbirths. Salihu and associates, in an analysis of national vital statistics, documented that 1.8% of twin, 2.4% of triplet, 3.7% of quadruplet and 5.6% of quintuplet fetuses suffered intrauterine fetal deaths [59]. The stillbirth rate among singleton pregnancies is approximately 0.5%.

The stillbirth rate is higher in the trailing fetus(es) than in the presenting fetus [60]. Although unproven, this is teleologically more likely a function of the condition(s) that led to the presenting fetus being presenting rather than a simple mechanical or positional issue. The causes of fetal deaths in multiple gestations are far less clear than in singleton pregnancies. However, fetal growth restriction, abruption, preeclampsia, anomalies and cord accidents are all more common in multiple gestation and are likely etiologic. It is important to establish the chorionicity of multiple gestations, as the stillbirth rate is higher in monochorionic multiple gestations [61,62]. This is likely related to the superficial and deep placental vascular anastamoses that characterize the monochorionic multifetal placenta [63].

Assisted reproductive technology (ART) is associated both with an increased incidence of multiple gestation and stillbirth. However, it remains uncertain whether multiple gestations conceived with ART are at increased risk of stillbirth [64,65]. If such an association exists, it may merely reflect that fact that some couples who rely on ART may suffer from a type of infertility that may be independently associated with stillbirth (e.g., repeated fetal losses).

Stillbirth and fetal growth restriction

Stillbirth pregnancies are associated with increased prevalence of small for gestational age (SGA) fetuses compared with live births. In fact, the risk of stillbirth increases with declining percentile of birth weight [66]. However, it is fetal growth impairment and not small fetal size that is associated with stillbirth. Unlike SGA fetuses, the fetuses with impaired growth are those that are smaller than expected after physiologic factors determining fetal size were considered. A study of over 300,000 pregnancies clearly demonstrated that stillbirth is more frequent only among those fetuses [67]. The cross-sectional studies of association between fetal size and growth and stillbirth have a significant limitation. The time of death is not precisely known and gestational age at delivery might be considerably longer than at the time of demise, falsely increasing incidence of SGA and growth restricted fetuses. Despite this uncertainty, the relation between fetal growth impairment and stillbirth seems real. Several recent studies demonstrated strong, “dose dependent” and biologically plausible associations between concentration of early or mid-pregnancy placental hormones and stillbirth [68–70].

Umbilical cord accidents

A substantial proportion of stillbirths are attributed to umbilical cord “accidents,” thought to occur due to cord occlusion from true knots, nuchal cords or cord compression. However, up to 30% of normal pregnancies are complicated by nuchal cords and true knots in the umbilical cord are often detected in association with live born infants. In a Swedish population-based survey, nine percent of stillbirths were attributed to cord accidents.[26] In contrast, autopsy case series ascribe fetal death to cord accident at lower frequency (up to 2.5%).[71,72] This discrepancy suggests that, absent other obvious abnormalities (and often without histopathologic examination of placenta or fetus) fetal death is often ascribed to cord entanglement.

The prejudice that cord “accident” may contribute to stillbirth is self-reinforcing. A case-control study of “unexplained” stillbirths matched by maternal race, year of birth, plurality, sex and birth weight demonstrated an odds ratio for “cord problems” of 6.6 (C.I. 1.4–31.8), yet paradoxically reduced odds of medical and other obstetrical complications.[73] These data raise the possibility that such attribution may only reflect inadequate diligence in identifying explanatory familial, medical or histological associations. In order to convincingly attribute a stillbirth to cord accident, it is necessary to demonstrate cord occlusion, hypoxic tissue injury on autopsy, and exclude other accepted causes of stillbirth. These conditions are rarely met. Taken together with the frequency of nuchal cords in normal pregnancies, the actual proportion of stillbirths due to cord accidents remains uncertain.

Obstetric complications—A variety of obstetric complications directly or indirectly contribute to stillbirth. Examples include preeclampsia, preterm premature rupture of membranes, preterm labor, cervical insufficiency, abruption, placenta previa, and vasa previa. It is estimated that abruption accounts for 10 – 19% of stillbirths [74,75]. The precise contribution of other obstetric complications such as cervical insufficiency or preterm labor to stillbirth is uncertain. In most cases, these conditions lead to neonatal demise rather than stillbirth. However, occasionally death will occur prior to delivery in the setting of these conditions. These obstetric complications may occur as a primary problem, or as a secondary complication of another condition (e.g. abruption associated with cocaine use or preeclampsia in the setting of antiphospholipid syndrome or triploidy).

EVALUATION OF STILLBIRTH

The optimal evaluation of stillbirth is controversial and is influenced by several medical and non-medical factors. First, the true proportion of stillbirths due to any single etiology is largely

unknown due to a relative lack of comprehensive, population based studies and debate regarding the definitive attribution of a stillbirth to a particular etiology. Second, many causes of stillbirth remain to be elucidated and investigation into previously unrecognized causes of stillbirth has been limited. Third, stillbirth is an emotionally charged event and different families and cultures will have varied levels of comfort with procedures such as autopsy or genetic testing. Finally, in most settings, cost of testing must be considered prior to initiating a comprehensive evaluation for potential causes of stillbirth.

When deciding which tests are most useful, two principles seem appropriate to consider. First, it is most cost effective to test for the most common causes of stillbirth. Second, it is desirable to identify conditions that predispose couples to recurrent stillbirth as opposed to sporadic pregnancy loss. This is especially true for conditions wherein medical intervention may prevent recurrent stillbirth. Although preference should be given to common, recurrent, and preventable disorders, there is still value to the identification of sporadic conditions. Identifying a sporadic cause of stillbirth helps bring emotional closure to couples and provides reassurance in future pregnancies. The identification of a sporadic cause of stillbirth also may allow couples to avoid unnecessary tests and interventions in subsequent pregnancies.

We recognize that the generally accepted or recommended evaluation for stillbirth differs among experts and that clear data are lacking. Ongoing studies such as those conducted by the Stillbirth Collaborative Research Network (see below) should help guide future management. Meanwhile, clinicians need to “do the best we can” with available information. It is noteworthy that the proportion of stillbirths that are “explained” is much higher in centers using systematic evaluations for recognized causes and potential causes of stillbirth [26,74]. Indeed, and although subject to some legitimate debate regarding causality, some centers have been able to determine a cause in 25 – 90% of cases [26,74].

Perhaps the single most useful diagnostic test is a fetal autopsy [14]. In addition to the identification of birth defects and morphologic abnormalities suggesting genetic or developmental abnormalities, autopsy can determine and/or confirm numerous other causes of stillbirth. Examples include infection, anemia, hypoxia, and metabolic abnormalities. The use of fetal autopsy has been limited in many institutions by cost, a lack of trained pathologists, and discomfort on the part of physicians and patients in discussing or having the procedure. Clinicians can reduce these problems by recognizing the value of the test, facing their own discomfort, and frankly addressing families concerns about autopsy. It is often possible to work with individuals emotional and religious needs while still accomplishing an informative autopsy. It is helpful to ask families about their specific concerns and reasons for refusing autopsy. In many instances, their fears can be alleviated with education or modification of the procedure. In cases wherein autopsy is refused, partial autopsy or post-mortem MRI may provide substantial information [76].

Ideally, national efforts will be made to increase the number of pathologists with expertise in perinatal pathology and funding for perinatal autopsies. Meanwhile, clinicians may raise interest and quality in their local pathologists by discussing clinical cases with them prior to autopsy. Providing the pathologist with a good clinical history is invaluable in guiding an appropriate investigation into potential causes of stillbirth. Hospital programs that cover the cost of fetal autopsies provide good will for the hospital. Finally, tissue blocks may be sent to pathologists with special expertise at other institutions when local physicians cannot provide an adequate evaluation.

Histologic evaluation of the placenta, membranes, and umbilical cord also is quite valuable. This can provide insight into many different potential etiologies of stillbirth including infection, genetic abnormalities, anemia, and thrombophilias. As with autopsy, trained pathologists and

a scientific, systematic evaluation are critical. It is noteworthy that placental evaluation is increasingly advised for medico-legal purposes in all cases of adverse perinatal outcome (e.g. preterm birth) including stillbirth [77]. It is rare for families to refuse placental evaluation.

Fetal karyotype is valuable, especially in cases wherein autopsy is not performed. As stated earlier, chromosomal abnormalities are present in at least 6 – 12% of stillbirths [12,13]. The risk of an abnormal karyotype is higher for fetuses with structural abnormalities, dysmorphic features, or those dying earlier in gestation. These risk factors may be used to stratify risk if cost is an issue. A case can be made for health care insurers to pay for the procedure, given that the risk of abnormality is substantially higher than for most cases of antenatal genetic testing. Tissues most likely to provide cells that can successfully be grown in culture include placenta (especially chorionic plate), fascia lata, skin from the nape of the neck, and tendons. Ideally, a trained pathologist should send tissues for karyotype after gross evaluation of the fetus and placenta. If this is not possible, clinicians should take care to not place placental or fetal tissues in formalin so that attempts can be made to culture cells. Comparative genomic hybridization shows tremendous promise for the identification of chromosomal abnormalities in stillbirths wherein fetal cells cannot be successfully cultured [13]. In cases of unsuccessful cell culture, clinicians should investigate whether or not comparative genomic hybridization is available in their center.

As stated earlier, genetic abnormalities not identified by karyotype almost assuredly contribute to some cases of stillbirth. Additional genetic testing for specific conditions may be appropriate based on suspicion raised through perinatal autopsy. However, widespread testing for single gene disorders, microdeletions, and confined placental mosaicism is still considered experimental and the evidence to offer these tests on a routine basis is lacking.

The most convincing proof of an infectious etiology for a stillbirth is a carefully-performed autopsy and histologic evaluation of the placenta, membranes and umbilical cord. The pathologist may then proceed with appropriate cultures and nucleic acid specimens (for bacteria or viruses) taken for organisms suspected based on histology. It is controversial as to whether or not routine cultures or serology are useful in the evaluation of stillbirth. Parvovirus serology may be useful since this virus has been implicated in a meaningful proportion of cases [20]. Screening for syphilis also is advised, as this organism is a generally accepted cause of stillbirth. Serology for intrauterine viral and protozoal agents including toxoplasmosis, rubella, CMV, herpes (so-called TORCH organisms) is of questionable utility. Although traditionally advised in the evaluation of stillbirth, these titers are rarely clinically useful in the United States (anecdotal experience). Similarly, although routine bacterial culture of the placenta may prove useful, it can be problematic. It is important to avoid vaginal wall contamination by culturing in between the membranes. It may be useful to culture for ureaplasmas and mycoplasmas in addition to aerobic and anaerobic cultures. However, the incidence of positive cultures in live-born pregnancies is unknown. Nucleic acid based tests for bacterial or viral products in the fetus or gestational tissues are often more sensitive than culture. While this may identify additional cases of infection, it may also lead to more “false positive” results.

Fetal-maternal hemorrhage is a common cause of stillbirth and screening for this potential cause is advised. The Kleihauer-Betke test (KBT) is used for the detection of fetal erythrocytes in maternal blood. This method is based on elution of adult hemoglobin (HbA) from adult red cells, whereas the more acid-resistant fetal hemoglobin (HbF) remains intact in fetal red cells. This remaining hemoglobin is subsequently visualized by staining with erythrosin. Although manual KBT is used by most labs, there is statistical imprecision in quantifying FMH due to evaluating low numbers of cells, resulting in underestimation of fetal cell count in cases of large FMH [27]. Flow cytometry may be more accurate than the KBT and is used by some centers to identify fetal red cells in the maternal circulation.

Indirect Coombs' test is advised to exclude red cell alloimmunization as a cause of stillbirth. Autopsy and placental evaluation also are helpful in evaluating this condition. If the antibody screen at the initial prenatal visit is negative, repeat testing is unnecessary. Sensitization during the current pregnancy is exceedingly unlikely to result in stillbirth.

Routine testing for antiphospholipid syndrome and/or heritable thrombophilias is controversial. Testing cases characterized by placental insufficiency seems appropriate given the apparent pathophysiology of the conditions. There is limited evidence [78]that treatment in subsequent pregnancies may improve outcome in women with prior stillbirth and these conditions. Accordingly, enthusiasm is considerable for identifying patients with these disorders. However, some heritable thrombophilias are present in a very large proportion of normal individuals and a positive test may be unrelated to the stillbirth. Thus, caution must be used before adopting widespread testing. There is evidence to support limiting thrombophilia testing to cases with 1) evidence of placental insufficiency such as IUGR or placental infarction, 2) recurrent fetal loss, or 3) personal or family history of thrombosis.

Clinically overt diabetes and thyroid disease should be excluded. However, screening for subclinical disease is of unproven benefit. Routine testing for TSH or glycohemoglobin is not advised pending additional data regarding utility.

Illicit drug use accounts for a meaningful proportion of stillbirths. Thus, routine toxicology screen is appropriate in most centers. This is most easily accomplished with a comprehensive urinary screen. However, it is now possible to measure stable metabolites of many recreational substances in numerous tissues including meconium, [79] hair, [80] and homogenized umbilical cord[81].

The importance of a good clinical evaluation should not be overlooked when ordering diagnostic tests. Careful medical and obstetric history and physical examination can identify medical conditions, infections, recurrent placental insufficiency, abnormal serum screens, etc. This may prove valuable in guiding the pathologist performing autopsy and placental evaluation. It also may identify epidemiologic risk factors such as smoking, stress, age, etc.

Table IV summarizes the evidence for the diagnostic evaluation of stillbirth. In summary, autopsy, placental evaluation, karyotype, Kleihauer-Betke, antibody screen, and serologic test for syphilis are useful in the workup of stillbirth. Other tests should be considered in selected cases. It is uncertain whether it is preferable to test for potential causes of stillbirth in a sequential, rather than comprehensive manner. Sequential testing has the potential benefit of cost savings and the avoidance of positive results that cause anxiety and do not identify a true etiology of stillbirth (e.g. thrombophilia in the setting of normal fetal growth). On the other hand, some cases may be due to more than one cause or the interaction of several causes or risk factors. This may only be identified through comprehensive testing. Another consideration is that autopsy, placental evaluation, karyotype, screen for fetal-maternal hemorrhage, and toxicology screen are time dependent and cannot be done long after delivery. We hope that ongoing studies including the Stillbirth Collaborative Research Network will help to clarify the optimal diagnostic work up of stillbirth. A discussion of the management of subsequent pregnancies in women with prior stillbirth is beyond the scope of this paper.

SCRN description

The National Institute of Child Health and Human Development (NICHD) established the Stillbirth Collaborative Research Network (SCRN) to study the scope and causes of stillbirth in the United States. The Stillbirth Collaborative Research Network (SCRN) will address three overarching hypotheses:

1. The use of standardized surveillance in a geographic catchment area will show that the stillbirth rates are greater than those reported in the vital statistics catchment.
2. The use of a prospectively implemented, standardized, postmortem and placental examination protocols will improve diagnosis of fetal or placental conditions that cause or contribute to stillbirth.
3. Maternal biologic and environmental risk factors in combination with genetic predisposition increase the risk for stillbirth

A multi-site, population-based, hypothesis-driven, case cohort and nested case-control study of prospectively enrolled stillbirths and live births will be conducted, with representation from rural and urban areas and diverse ethnic/racial groups.

Investigators at each of five clinical sites have defined geographic catchment areas by state and county lines. The clinical sites are: Brown University, Rhode Island; Emory University, Georgia; University of Texas Medical Branch at Galveston, Texas; University of Texas Health Sciences Center at San Antonio, Texas; University of Utah Health Sciences Center, Utah.

Acknowledgments

This work was supported, in part, by grant funding from the Stillbirth Collaborative Research Network sites: U10-HD045953 Brown University, Rhode Island; U10-HD045925 Emory University, Georgia; U10-HD045952 University of Texas Medical Branch at Galveston, Texas; U10-HD045955 University of Texas Health Sciences Center at San Antonio, Texas; U10-HD045944 University of Utah Health Sciences Center, Utah; and U01-HD045954 RTI International, RTP.

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Table I

Wigglesworth classification[5]

1	Congenital defect/malformation (lethal or severe)
2	Unexplained antepartum fetal death
3	Death from intrapartum ‘asphyxia’, ‘anoxia’ or ‘trauma’
4	Immaturity
5	Infection
6	Death due to other specific causes
7	Death due to accident or non-intrapartum trauma
8	Sudden infant death, cause unknown
9	Unclassifiable

Table II

ReCoDe (**Re**levant **C**ondition of **De**ath) classification[10]

- **A. Fetus**
  - **1.** Lethal congenital anomaly
    - **a.** Infection
    - **b.** Chronic – e.g. TORCH
    - **c.** Acute
  - **2.** Non-immune hydrops
  - **3.** Iso-immunisation
  - **4.** Fetomaternal hemorrhage
  - **5.** Twin-twin transfusion
  - **6.** Intrapartum asphyxia
  - **7.** Fetal growth restriction
  - **8.** Other
- **B. Umbilical Cord**
  - **1.** Prolapse
  - **2.** Constricting loop or knot
  - **3.** Velamentous insertion
  - **4.** Other
- **C. Placenta**
  - **1.** Abruptio
  - **2.** Previa
  - **3.** Vasa Previa
  - **4.** Placental infarction
  - **5.** Other placental insufficiency
  - **6.** Other
- **D. Amniotic fluid**
  - **1.** Chorioamnionitis
  - **2.** Oligohydramnios
  - **3.** Polyhydramnios
  - **4.** Other
- **E. Uterus**
  - **1.** Rupture
  - **2.** Uterine anomalies
  - **3.** Other
- **F. Mother**
  - **1.** Diabetes
  - **2.** Thyroid diseases
  - **3.** Essential Hypertension
  - **4.** Hypertensive diseases in pregnancy
  - **5.** Lupus/Antiphospholipid Syndrome
  - **6.** Cholestasis
  - **7.** Drug abuse
  - **8.** Other
- **G. Trauma**

1. External
2. Iatrogenic

H. Unclassified

1. No relevant condition identified
2. No information available

Table III

Proposed "Definite" causes of death

- **Maternal death**
  - unintentional injuries
    - Toxic (including teratogenic) injury
    - Physical injury
  - Homicide
  - Suicide
  - Complications of medical and surgical care
    - Therapeutic drug or radiation exposure during pregnancy
    - Intra-gestational uterine surgery
  - Diseases that cause maternal death during pregnancy
    - Neoplasia
    - Cardiovascular diseases
    - Hematological diseases
    - Infectious diseases
- **Birth injuries**
  - Uterine rupture
  - Dystocia or malpresentation
    - Attempted instrumental vaginal delivery
    - Without attempted instrumental vaginal delivery
- **Placental lesions (excluding infection)**
  - Umbilical cord lesions with clinical and/or histologic evidence of umbilical cord vessel obstruction
    - Umbilical cord prolapse
    - True knots with evidence of circulatory compromise
    - Strangulation due to long cord
    - Furcate insertion
    - Velamentous insertion
    - Neoplasms of the umbilical cord
  - Lesions involving the placental parenchyma
    - Abruptio placenta
    - Intraparenchymal thrombi/fibrin deposition involving the entire placental parenchyma
    - Infarction of the entire placental parenchyma
    - Neoplasms or developmental lesions involving the entire placental parenchyma
      - Mesenchymal dysplasia
      - A-V malformations etc.
- **Hydrops fetalis, marked, immune or non-immune Complications multiple gestation**
  - Twin-twin transfusion syndrome (Advanced stage)
  - TRAP (twin reversed arterial perfusion) sequence
  - Strangulation due to umbilical cord entanglement (Monoamnionic-monochorionic gestations)
- **Lethal congenital developmental conditions**
  - Fetal aneuploidy
    - Chromosome 19, mosaic trisomy 19
    - Tetraploidy 92XXXX,92XXYY

- Triploidy 69XXX,69XXY
- Bony dysplasias with thoracic constriction and evidence of hemodynamic compromise.
  - Achondrogenesis
  - Asphyxiating thoracic dysplasia
  - Camptomelia, short gut, polycystic kidney/liver, polysplenia
  - Chondrodysplasia sequences
  - Hypochondrogenesis
  - Osteogenesis imperfecta congenita IIa
  - Short rib-polydactyly syndromes
  - Spondylohypoplasia, arthrogryposis, popliteal pterygium
- Fetal akinesia sequence
- Lethal multiple pterygium syndrome

Infections

- Chronic fetal/placental infection, fulminant
  - Syphilis
  - Rubella
  - Toxoplasmosis
  - Cytomegalovirus
- Acute fetal/placental infection, fulminant
  - Herpes simplex
  - Varicella
  - Cytomegalovirus

Table IV

Status of evaluation for stillbirth

Generally accepted tests:
Fetal autopsy
Placental evaluation
Karyotype
Indirect Coombs’
Serologic test for syphilis
Screen for fetal-maternal hemorrhage (Kliehauer-Betke or other)
Toxicology screen
Thorough medical and obstetric history
Parvovirus serology
Useful in some cases:
Lupus anticoagulant screen
Anticardiolipin antibodies
Factor V Leiden mutation
Prothrombin G20210A mutation
Screen for protein C, protein S, and antithrombin III deficiency
Uncertain utility:
TSH
Glycohemoglobin
TORCH titers
Placental cultures
Testing for other thrombophilias
Developing technology:
Comparative genomic hybridization
Testing for single gene mutations
Testing for confined placental mosaicism
Nucleic acid based testing for infection