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Stillbirth Associated With Infection in a Diverse U.S. Cohort

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OBJECTIVE: To better characterize infection-related stillbirth in terms of pathogenesis and microbiology.

METHODS: We conducted a secondary analysis of 512 stillbirths in a prospective, multisite, geographically, racially and ethnically diverse, population-based study of stillbirth in the United States. Cases underwent evaluation that included maternal interview, chart abstraction, biospecimen collection, fetal autopsy, and placental pathology. Recommended evaluations included syphilis and parvovirus serology. Each case was assigned probable and possible causes of death using the INCODE Stillbirth Classification System. Cases where infection was assigned as a probable or possible cause of death were reviewed. For these cases, clinical scenario, autopsy, maternal serology, culture results, and placental pathology were evaluated.

RESULTS: For 66 (12.9%) cases of stillbirth, infection was identified as a probable or possible cause of death. Of these, 36% (95% CI 35–38%) were categorized as a probable and 64% (95% CI 62–65%) as a possible cause of death. Infection-related stillbirth occurred earlier than non–infection-related stillbirth (median gestational age 22 vs 28 weeks, P=.001). Fetal bacterial culture results were available in 47 cases (71%), of which 35 (53%) grew identifiable organisms. The predominant species were *Escherichia coli* (19, 29%), group B streptococcus (GBS) (8, 12%), and enterococcus species (8, 12%). Placental pathology revealed chorioamnionitis in 50 (76%), funisitis in 27 (41%), villitis in 11 (17%), deciduitis in 35 (53%), necrosis in 27 (41%), and viral staining in seven (11%) cases. Placental pathology found inflammation or evidence of infection in 65 (99%) cases and fetal autopsy in 26 (39%) cases. In infection-related stillbirth cases, the likely causative non-bacterial organisms identified were parvovirus in two (3%) cases, syphilis in one (2%) case, cytomegalovirus (CMV) in five (8%) cases, and herpes in one (2%) case.

CONCLUSION: Of infection-related stillbirth cases in a large U.S. cohort, *E coli*, GBS, and enterococcus species were the most common bacterial pathogens and CMV the most common viral pathogen.

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In the United States, stillbirth (defined as fetal death at or after 20 weeks of gestation) affects about 1 in 168 pregnancies (6/1,000 pregnancies) or 23,595 per year based on 2015 data.[1] Causes of stillbirth include genetic abnormalities, obstetric complications, maternal medical diseases and abnormalities of the placenta and umbilical cord. Maternal or fetal infection (or both) is an important cause of fetal death for which prospective, well-characterized studies are lacking. Approximately 10–20% of stillbirths have been reported to be caused by infection in high-income countries.[2,3] The percentage is likely higher in low-income countries.[2]

The proportion of stillbirths due to infection is uncertain because clinical symptoms or signs of infection may not be apparent and because systematic evaluation for infection is not always conducted when assessing stillbirth. In addition, although many organisms have been reported to cause sporadic stillbirths, large studies have not reported the specific responsible organisms. Thus, our primary objective was to evaluate and characterize stillbirth related to infection using clinical, histologic, and microbiologic data. We also sought to characterize the organisms associated with stillbirth, as well as the utility of various tests for the identification of infection-related stillbirth, in a well-characterized, large and diverse U.S. cohort.

METHODS

The Stillbirth Collaborative Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development conducted a multi-center, ethnically, racially, and geographically diverse case–control study including stillbirths and a representative sample of live births enrolled in five catchment areas defined by county boundaries between March 2006 and September 2008. Detailed methods have previously been published.[4] Stillbirth was defined as death at the time of delivery at or after 20 weeks of gestation with Apgar scores of 0 and 0 at 1 and 5 minutes. Gestational age was determined by multiple sources and an algorithm as previously described.[4] Participants gave written informed consent and Institutional Review Board approval was obtained from each clinical site and the data-coordinating center.

The protocol included medical record abstraction, maternal interview, biospecimen collection, and placental pathologic examination for all participants, with postmortem examination of stillbirths, which included freezing sections of placenta and membranes in stillbirths and live births and liver in stillbirths.[5,6] Sections of frozen placenta and liver were stored at −80°C. In cases of stillbirth, clinicians were advised to obtain a standard set of "clinically indicated" laboratory studies.[7] These included serologic tests for syphilis and parvovirus as well as tests to assess noninfectious causes of stillbirth.[4] However, all of these tests were not obtained in every case of stillbirth, resulting from either patient or health care provider preference or lack of stored serum sample.[3,8] Parvovirus serology also was assessed using maternal sera collected at the time of enrollment in cases that did not have previous testing. ELISA was used to determine whether parvovirus immunoglobulin (Ig)M and IgG antibodies were present.

Each stillbirth was assigned a cause of death using an algorithm developed by the Stillbirth Collaborative Research Network investigators, termed INCODE (initial causes of fetal death).[9] The algorithm was designed to account for the facts that causes of stillbirth are often uncertain and that multiple factors may contribute. Conditions were considered to either be "probable" or "possible" causes of stillbirth, or present but unlikely to be contributors to the stillbirth.[9] Probable causes were conditions with a high likelihood of directly causing the stillbirth based on the best available evidence at the time INCODE was developed. An example of this would be a case in which fetal hydrops is present and parvovirus is identified on maternal serology or placental and fetal pathology. Possible causes were those that were possibly involved in a pathophysiologic sequence that led to the death, without being a direct cause of the stillbirth, such as a case in which there is histologic evidence of infection in vital organs without culture or polymerase chain reaction (PCR)-proven infection. If a condition associated with stillbirth was ascertained but did not meet criteria for probable or possible cause, it was considered "present." For example, a case in which a culture or PCR result was positive for infection, but no histologic or clinical infectious sequelae were noted would be classified as present. In the initial analysis of causes of death among 512 stillbirths, infection was determined to be a probable or possible cause in 66 (12.9%) cases.[8] Of these, 65% were antepartum and 35% were intrapartum stillbirths. Infection accounted for a higher proportion of stillbirths relatively early in gestation, especially before 23 weeks of gestation, and were associated with a higher percentage of stillbirths in non-Hispanic black women compared with non-Hispanic white women or Hispanic women.[8] Our primary analysis includes specific details of these 66 cases with probable or possible infectious causes of stillbirth. After our review, one case was excluded from our analysis after

a second review of the INCODE cause of death was not consistent with a possible or probable infection cause of death. Another case was included as a possible infection cause of death as it was twin B of a pregnancy in which twin A had a possible infection cause of death.

We also categorized the pathophysiologic pathway to infection-related stillbirth based on the clinical scenario and results of serology and histologic examinations. These pathways include direct fetal infection; direct fetal infection causing fetal anomalies or pathologic condition; placental infection leading to placental insufficiency; severe maternal illness; infection involved in a previable or periviable preterm birth; and cases of isolated placental inflammation.[2,9] Direct fetal infection was defined by evidence of fetal infection on blood or lung cultures as well as inflammation on histologic fetal examination. Cases with infections that can cause a fetal anomaly or malformation (eg, cytomegalovirus [CMV] or parvovirus) were designated by findings of these organisms on culture or histology or by pathognomonic findings in the fetus or placenta. Cases with culture or PCR-proven infection in combination with placentitis or villitis or pathognomonic findings of an organism known to cause placental inflammation leading to placental insufficiency (eg, syphilis) were categorized into this group. Severe maternal illness was defined by documented maternal infection process leading to systemic shock (ie, hypotension, end organ injury) or need for intensive care unit admission. Cases in which infection was involved in a preterm labor process (preterm prelabor rupture of membranes, cervical insufficiency, preterm contractions) at a previable or periviable gestational age were included in the preterm labor group. Cases for which isolated placental inflammation was noted without fitting into one of the above groups were categorized as placental inflammation only. Records were individually reviewed to verify the clinical history and test results for all cases included in this analysis.

Characteristics were compared between those with and without infection among stillbirths as well as between stillbirths with infection and a live-birth control group. The sampling design of the study was taken into account with SAS survey procedures and weighting adjustment for the staggered start for enrollment at the 59 hospitals and differential participation rates in the study design to ensure that the control group (live births) was representative of the delivery population of the catchment area as previously described.[4] The Rao-Scott χ^2 test or Fisher exact test were used for all categorical univariate comparisons and the f-test for numeric univariate comparisons. The utility of a diagnostic test to determine a probable or possible cause of death was determined in this cohort of cases. A test result was considered a "pertinent positive" if it detected a cause of death or confirmed a cause of death that was suspected based on clinical presentation. A "pertinent negative" test was defined as a result that ruled out a potential cause of death based on the clinical scenario.[10]

RESULTS

A total of 663 women with 676 stillbirths were enrolled; of these, 500 women with 512 stillbirths that had complete fetal postmortem examination were included in this analysis (Fig. 1). Characteristics of this cohort have previously been described.[8] Among the 500 women, 495 (99.0%) had serologic testing for syphilis, 451 (90.2%) for parvovirus, 38 (7.6%) for CMV, and 56 (11.2%) for toxoplasmosis. Results of vaginal culture for group B streptococcus (GBS) were available for 105 (20.5%).

In stillbirths at 37 weeks of gestation or greater, 75.0% of cases had GBS results (63/84 cases). Of the cases with a probable or possible infection cause of death, fetal bacterial culture results (obtained at the discretion of the pathologist from fetal blood and lung) were available in 47 cases, of which 35 had growth and identification of various organisms. The remaining cases did not have culture data available. Of the cases of stillbirth thought to be due to infection, five (8%) had placental culture results with polymicrobial growth that in most cases did not correlate with the clinical scenario or likely pathogenic organism. In this study, placental cultures were not systematically obtained. Accordingly, these findings should be interpreted with caution.

In the 66 infection-related stillbirths, 36% (95% CI 35–38%) were categorized as a probable infection-related stillbirth and 64% (95% CI 62–65%) as a possible infection-related stillbirth. Of these, 21 (32%) had infection as the only cause of death suspected. There were 45 (68%) stillbirths with more than one possible or probable cause of death including infection. In the multifactorial cases, spontaneous preterm delivery at nonviable gestation ages occurred in 31 (69%) cases, followed by placental (11, 24%), genetic (5, 11%), maternal medical conditions (5, 11%), other causes (3, 7%), hypertensive disorders (2, 4%) and umbilical cord causes (2, 4%). Infection-related stillbirths occurred at lower gestational ages (P=.001), were more often intrapartum (P<.001) and were more frequent in non-Hispanic black race–ethnicity (P<.001) as compared with non–infection-related

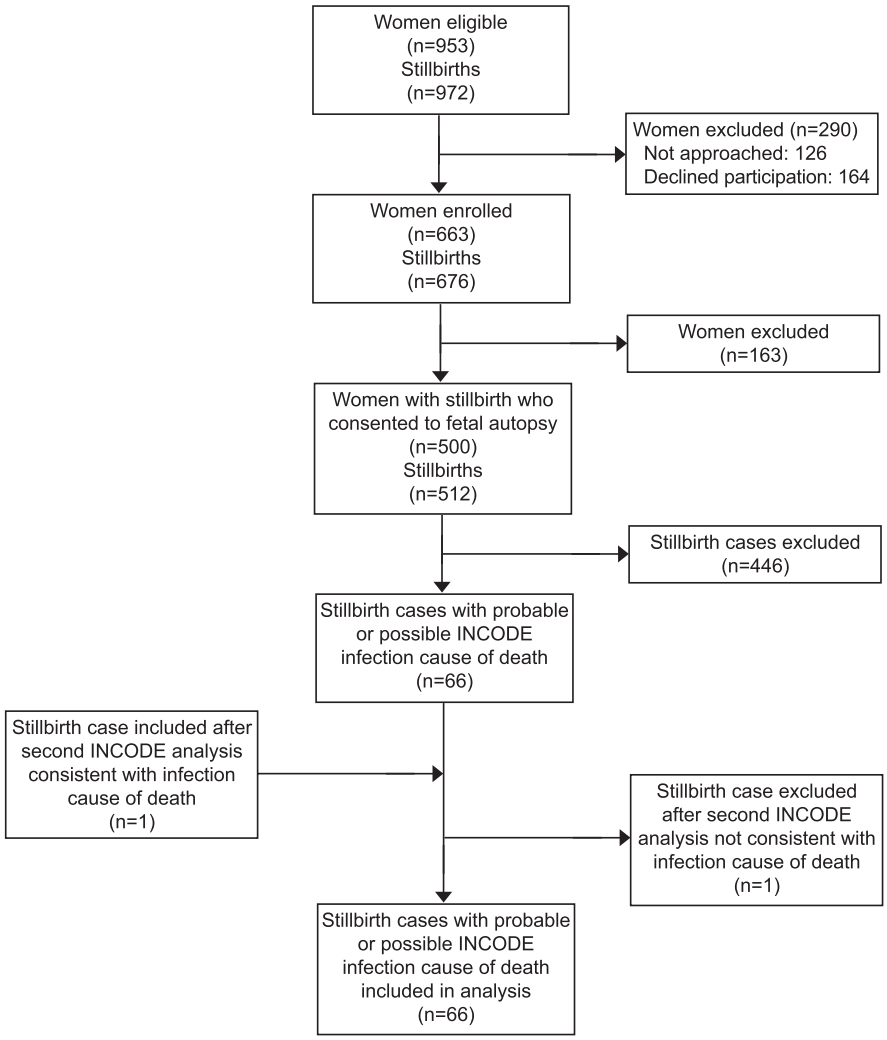

Fig. 1. Enrollment of stillbirths. INCODE, initial causes of fetal death. Live birth enrollment: 3,083 women identified; 394 (13%) not approached; 759 (25%) declined to participate; 1,930 (63%) consented for the study. Ref. 4 details the complete study design and recruitment experience of the parent study.

Page. Infection-Related Stillbirths. Obstet Gynecol 2019.

stillbirths (Table 1). As compared with live births by gestational age, infection-related stillbirth was more common among non-Hispanic black women ($P<.001$) and was less often associated with hypertensive disorders of pregnancy ($P=.002$; Table 2).

The predominant organisms responsible for probable and possible causes of infection-related death, stratified by timing of stillbirth were *Escherichia coli* (19, 29%), GBS (8, 12%), and enterococcus species (8, 12%). Most cases occurred before 24 weeks of gestation (59%), with 11% at 24–28 weeks, 5% at 29–31 week, 12% at 32–36 weeks, and 14% at 37–42 weeks (Table 3).

The most useful tests were placental pathology and fetal autopsy with a pertinent positive result in 89% and 55% of cases respectively (Table 4). In the 66 cases, placental pathology revealed chorioamnionitis in 50 (76%), funisitis in 27 (41%), villitis in 11 (17%), deciduitis in 35 (53%), necrosis in 27 (41%), and viral staining or inclusion bodies in seven (11%) cases. Overall, placental pathology found inflammation or evidence of infection in 65 (99%) cases. Fetal autopsy detected inflammation or evidence of infection in 26 (39%) cases.

Serologic tests used as a "screen" for infection did not increase the diagnostic yield in any cases (Table 4). In infection-related stillbirths (n=66), five cases had a positive serologic result (positive IgM) for parvovirus. However, in three of these cases there was no evidence of parvovirus infection clinically or on placental pathology and fetal autopsy. Thus, parvovirus infection was not considered to be a probable or possible cause of death and the test was not "useful" in the diagnostic evaluation.

Fetal cultures (blood, lung) provided a pertinent positive result in 53% of cases tested with yield limited by contamination or lack of growth in many cases. Data regarding placental cultures were available for

Table 1. Characteristics of Non–Infection-Related Stillbirths and Infection-Related Stillbirths

	Stillbirth, No Infection (n=446)	Infection-Related Stillbirth (n=66)	*P*
Maternal age (y)			.555
Younger than 20	54 (12.1)	6 (9)	
20–34	321 (72.0)	53 (80)	
35–39	53 (11.9)	5 (8)	
40 or older	18 (4.0)	2 (3)	
Gestational age (wk)	28 (23, 35)	22 (21, 32)	.001
Intrapartum stillbirth			<.001
Intrapartum	63 (14.1)	24 (36)	
Antepartum	383 (85.9)		
Maternal race–ethnicity			<.001
White, non-Hispanic	171 (38.3)	12 (18)	
Black, non-Hispanic	86 (19.3)	29 (45)	
Hispanic	160 (35.9)	16 (25)	
Other	29 (6.5)	8 (12)	
Missing	0	1	
BMI (kg/m^2)			.488*
Less than 30	307 (71.1)	44 (69)	
30–39	96 (22.2)	17 (27)	
40–49	26 (6.0)	2 (3)	
50 or higher	3 (0.7)	1 (1)	
Missing	14	2	
Chronic hypertension			.485
Yes	46 (10.3)	5 (8)	
No	399 (89.7)	61 (92)	
Missing	1	0	
Preeclampsia or gestational hypertension			.292
Yes	48 (11.1)	4 (7)	
No	383 (88.9)	56 (93)	
Missing	15	6	
Pregestational diabetes			.558*
Yes	24 (5.4)	2 (3)	
No	421 (94.6)	64 (97)	
Missing	1	0	
Gestational diabetes			.758*
Yes	23 (5.2)	2 (3)	
No	423 (94.8)	64 (97)	
Insurance or method of payment			.367
No insurance	28 (6.3)	3 (5)	
Any public or private assistance	225 (50.7)	39 (60)	
Veterans Affairs, commercial health insurance, or HMO	191 (43.0)	23 (35)	
Missing	2	1	
Maternal education (y)			.577
0–11 (none, primary, some secondary)	87 (20.7)	16 (26)	
12 (completed secondary)	117 (27.9)	18 (29)	
13 or more (college)	216 (51.4)	28 (45)	
Missing	26	4	
Tobacco use			.268
None	343 (81.0)	51 (82)	
Fewer than 10 cigarettes/d	37 (8.8)	8 (13)	
10 or more cigarettes/d	43 (10.2)	3 (5)	
Missing	23	4	
Lifetime drug use			.309
Never used	294 (69.8)	39 (64)	

(*continued*)

Table 1. Characteristics of Non–Infection-Related Stillbirths and Infection-Related Stillbirths (*continued*)

	Stillbirth, No Infection (n=446)	Infection-Related Stillbirth (n=66)	*P*
Ever used, without addiction	110 (26.1)	17 (28)	
Ever used, with addiction	17 (4.1)	5 (8)	
Missing	25	5	

BMI, body mass index; HMO, health maintenance organization.
Data are n (column %), median (interquartile range), or n unless otherwise specified.
* Fisher exact test.

only a small subset of cases and may have been confounded by contamination. Accordingly, these results are not included in our analysis.

Of the overall Stillbirth Collaborative Research Network cohort of 512 stillbirth cases, there were few cases due to "TORCH" infections, a historic acronym for toxoplasmosis, syphilis (other), rubella, CMV, and herpes. These infections were assessed in the context of results from serologic screening (Table 4), histopathology and clinical correlates of infection. Cytomegalovirus was noted on placental pathology or fetal autopsy in six cases, and in five of these cases infection was a probable or possible cause of death. Acute parvovirus was the probable or possible cause of death in two cases in which nonimmune hydrops was present. Syphilis serology was found to be a probable cause of death in one case with spirochetes present on histologic examination. Herpes was the probable cause of death in one case with positive immunohistochemical staining on placental pathology. No cases of pathogenic toxoplasmosis, varicella-zoster or rubella were found, although these were not systematically evaluated. Of the nine cases in which TORCH infection was a probable or possible cause of death, all had positive findings either on placental pathology (eight/nine cases) or fetal autopsy (seven/nine cases). Cases with positive serology in the absence of findings on autopsy or placental histology were not identified as probable or possible infection-related causes of death.

In our analysis of pathophysiologic pathways leading to infection-related stillbirth, we found 10 cases (15%) of direct fetal infection and six cases (9%) of direct fetal infection involving an organism associated with fetal malformations. Of these latter six cases, four were due to CMV and two to parvovirus with fetal autopsy findings consistent with these infections. We identified five cases (8%) of placental infection leading to placental insufficiency including one case involving syphilis. There were no cases of severe maternal illness found after extensive medical record abstraction. We found 31 cases (47%) that fit primarily into the preterm birth pathophysiologic pathway. All cases with the exception of one occurred at a previable gestational age. The remaining 14 cases (21%) had only placental inflammation without characteristics fitting the above groups.

DISCUSSION

Of the 12.9% of cases of stillbirth probably or possibly due to infection, a majority (53%) were associated with bacterial pathogens. The most common organisms were *E coli*, GBS, and enterococcus species. There were eight viral infections (12%) including five with CMV, two with parvovirus B19, and one due to herpes virus as well as one case of syphilis.

In this study, parvovirus and syphilis were the only viruses and spirochetes that were systematically evaluated. Accordingly, we cannot make definitive conclusions regarding the prevalence of viral and spirochete pathogens in stillbirth cases overall. However, a positive viral serologic result in the absence of corresponding pathologic findings on fetal autopsy or placental histology is unlikely to represent a possible or probable cause of death. Therefore, our findings are likely accurate in regard to the relative paucity of known viral pathogens in comparison with bacterial organisms in infection-related stillbirth in the United States. Our data do not support routine screening for TORCH infections with maternal serology in the absence of other evidence for an infectious cause of stillbirth.

All cases of stillbirth linked to bacterial infection had abnormal findings suggestive of infection on placental histology, autopsy, or both. Our results suggest that fetal culture alone, in the absence of other findings suggestive of infection (clinical features, placental pathology, and fetal autopsy) are insufficient to support infection as a probable or possible cause of death. A suggested algorithm for the evaluation of infectious causes of stillbirth is shown in Figure 2.

Non-Hispanic black race was associated with infection-related stillbirth. In addition, stillbirth due to infection was more likely to occur at previable or

Table 2. Characteristics of Infection-Related Stillbirths and Live Births by Gestational Age

Variable	Less than 37 wk of Gestation			37 wk of Gestation or Greater		
	Infection-Related Stillbirths (Nw=55, n=54)	Live Births (Nw=155, n=485)	*P*	Infection-Related Stillbirths (Nw=10, n=10)	Live Births (Nw=1,285, n=1,447)	*P*
Maternal age (y)			.052			.132*
Younger than 20	3 (6)	16 (10.1)		2 (20)	133 (10.3)	
20–34	47 (85)	120 (77.5)		6 (60)	969 (75.4)	
35–39	4 (7)	15 (9.6)		1 (10)	157 (12.2)	
40 or older	1 (2)	4 (2.8)		1 (10)	26 (2.1)	
Maternal race–ethnicity			<.001			.040*
White, non-Hispanic	8 (14)	57 (36.6)		4 (40)	603 (46.9)	
Black, non-Hispanic	28 (52)	25 (16.5)		4 (40)	143 (11.2)	
Hispanic	13 (25)	64 (41.3)		1 (10)	438 (34.1)	
Other	5 (9)	9 (5.6)		1 (10)	101 (7.8)	
Missing	1	0		0	0	
BMI (kg/m^2)			.593*			.375*
Less than 30	34 (64)	100 (70.9)		10 (100)	964 (77.2)	
30–39	16 (31)	31 (22.2)		0 (0)	220 (17.6)	
40–49	2 (4)	8 (5.3)		0 (0)	56 (4.4)	
50 or higher	1 (1)	2 (1.6)		0 (0)	10 (0.8)	
Missing	2	14		0	35	
Chronic hypertension			.853			.999*
Yes	5 (9)	18 (11.7)		0 (0)	69 (5.4)	
No	50 (91)	136 (88.3)		10 (100)	1,206 (94.6)	
Missing	0	1		0	10	
Preeclampsia or gestational hypertension			.002			.999*
Yes	4 (8)	31 (21.3)		0 (0)	91 (7.3)	
No	47 (92)	116 (78.7)		10 (100)	1,152 (92.7)	
Missing	4	8		0	42	
Pregestational diabetes			.684*			.118*
Yes	1 (2)	7 (4.7)		1 (10)	15 (1.2)	
No	54 (98)	147 (95.3)		9 (90)	1,258 (98.8)	
Missing	0	1		0	12	
Gestational diabetes			.450*			.557*
Yes	1 (2)	8 (5.4)		1 (10)	98 (7.8)	
No	54 (98)	145 (94.6)		9 (90)	1,162 (92.2)	
Missing	0	2		0	25	
Insurance or method of payment			.101			.676*
No insurance	3 (6)	6 (4.1)		0 (0)	45 (3.5)	
Any public or private assistance	32 (59)	99 (64.1)		6 (60)	600 (46.8)	
Veterans Affairs, commercial health insurance, or HMO	19 (35)	49 (31.8)		4 (40)	638 (49.7)	
Missing	1	1		0	2	
Maternal education			.545		0.470*	
0–11 (none, primary, some secondary)	12 (23)	31 (21.9)		3 (40)	219 (17.9)	
12 (completed secondary)	17 (33)	53 (37.3)		1 (10)	299 (24.5)	
13 or more (college)	23 (44)	58 (40.8)		5 (50)	702 (57.6)	
Missing	3	13		1	65	
Tobacco use			.176*			.481*
None	43 (82)	125 (87.9)		7 (90)	1,060 (86.6)	

(*continued*)

Table 2. Characteristics of Infection-Related Stillbirths and Live Births by Gestational Age (*continued*)

Variable	Less than 37 wk of Gestation			37 wk of Gestation or Greater		
	Infection-Related Stillbirths (Nw=55, n=54)	Live Births (Nw=155, n=485)	*P*	Infection-Related Stillbirths (Nw=10, n=10)	Live Births (Nw=1,285, n=1,447)	*P*
fewer than 10 cigarettes/d	8 (15)	9 (6.3)		1 (10)	79 (6.5)	
10 or more cigarettes/d	2 (3)	8 (5.8)		0 (0)	84 (6.9)	
Missing	2	13		2	62	
Lifetime drug use			.494			.530*
Never used	31 (60)	94 (70.1)		7 (90)	840 (69.2)	
Ever used, without addiction	17 (32)	36 (26.7)		1 (10)	350 (28.8)	
Ever used, with addiction	4 (8)	4 (3.2)		0 (0)	24 (2)	
Missing	3	21		2	71	

Nw, weighted n; BMI, body mass index; HMO, health maintenance organization.
Data are n (column %) unless otherwise specified.
* Fisher exact test.

periviable gestational ages and to be associated with spontaneous preterm birth. There is considerable overlap in the pathophysiology of spontaneous preterm birth and many stillbirths associated with infection. Typically, this occurs when spontaneous preterm labor occurs at a previable or periviable gestation. This preterm labor process often leads to an intrapartum stillbirth, which often would have been avoided with interventions such as cesarean delivery at a later gestational age. Thirty-one (47%) cases in this cohort were due to this pathophysiologic sequence.

We performed a literature search using the search terms "stillbirth" and "infection." Existing data on infection-related stillbirth are comprised primarily of case series examining specific bacterial or viral pathogens with only a small number evaluating infection-related stillbirth in a prospective, comprehensive fashion. A study from Sweden noted positive cultures for *E coli*, *Enterococcus faecalis*, and GBS (as well as a likely contaminant, coagulase-negative staphylococcus species) in stillbirths.[11] There also were a number of organisms with very small numbers of positive cultures. It is not clear that infection was the unequivocal cause of death in all of these cases.[11] Several articles focused on GBS, because it causes serious neonatal morbidity and mortality in addition to stillbirth. A systematic review of 17 studies (most before 2000) noted a GBS-related stillbirth rate of 0.04–0.9 per 1,000

Table 3. Organisms Identified in Infection-Related Stillbirths From Fetal Culture, Stratified by Gestational Age

Variable	Gestational Age (wk)					Total
	Less Than 24	24 0/7–28 6/7	29 0/7–31 6/7	32 0/7–36 6/7	GA 37 or greater	
Total	39 (59)	7 (11)	3 (5)	8 (12)	9 (14)	66 (100)
Fetal culture results						
Positive	22 (33)	2 (3)	0	5 (8)	6 (9)	35 (53)
No growth	6 (9)	1 (2)	2 (3)	2 (3)	1 (1)	12 (18)
No data	11 (17)	4 (6)	1 (2)	1 (1)	2 (3)	19 (29)
Organisms found*						
Escherichia coli	13 (20)	0	0	2 (3)	4 (6)	19 (29)
GBS	5 (8)	0	0	2 (3)	1 (1)	8 (12)
Enterococcus species	4 (6)	2 (3)	0	1 (1)	1 (2)	8 (12)
Bacillus species	2 (3)	0	0	0	1 (2)	3 (5)
Enterobacter species	1 (2)	1 (1)	0	0	0	2 (3)
Other	12 (18)	3 (5)	0	2 (3)	1 (1)	18 (27)

GBS, group B streptococcus.
Data are n (%).
* Organisms are not mutually exclusive; 16 cases had multiple organisms present.

Table 4. Test Utility in Infection-Related Stillbirth Cases

Test	Total Tested (% of Total Infection Cases)	Positive Result (% of Cases Tested)	Pertinent Positive Result* (% of Cases Tested)	Normal Placental Pathology and Autopsy with Positive Screening Test (% of Cases Tested)
Test Utility in Stillbirths With a Possible or Probable Infection Cause of Death				
Placental pathology	66 (100)	63 (96)	59 (89)	NA
Fetal autopsy	66 (100)	36 (55)	36 (55)	NA
Parvovirus serology	55 (83)	5 (9)	2 (4)	3 (6)
Syphilis testing	65 (99)	1 (2)	1 (2)	0
CMV serology	11 (17)	2 (18)	2 (18)	0
HSV serology	16 (24)	2 (13)	1 (6)	0
Fetal cultures	47 (71)	35 (75)	25 (53)	0
Placental cultures	5 (8)	5 (100)	1 (20)	0

NA, not applicable; CMV, cytomegalovirus; HSV, herpes simplex virus.
Data are n (%).
* A pertinent positive result is a test result that confirms a clinically suspected cause of death or one that identifies a potential cause of death. Ref. 10 describes the methodology behind our assessment of test utility in stillbirth evaluation.

births.[12] The proportion of stillbirths associated with GBS was 0–12.1%.[12] Another systematic review and meta-analysis of 14 studies including five after 2000 noted that 1% (95% CI 0–2%) of stillbirths are associated with GBS in high income countries and 4% (95% CI 2–6%) in Africa.[13] Both studies acknowledge the low quality of available data.[12,13]

A lack of systematic cultures for infectious pathogens (including assessment of a panel of viral pathogens and identification of mycoplasmas and ureaplasmas) is a weakness of our study. It is possible that a more comprehensive approach could identify additional infectious causes of stillbirth. Also, molecular techniques such as PCR may identify additional causes of stillbirth. Strengths of the study include its prospective nature; unbiased enrollment; use of a control group; racial, ethnic, and geographic diversity; extensive and systematic evaluation including autopsy and placental histology in all cases; and use of a rigorous tool to assign causes of death.

In conclusion, most cases of infection-related stillbirth based on traditional clinical and pathologic criteria in a large and diverse U.S. cohort were associated with bacterial infections. The most common bacterial pathogens were *E coli*, GBS, and enterococcus species. We suggest that prevention efforts should target these organisms. To this end, the World Health Organization has research underway to develop a GBS vaccine, which would have a major effect on stillbirths and neonatal complications due to GBS worldwide.[14]

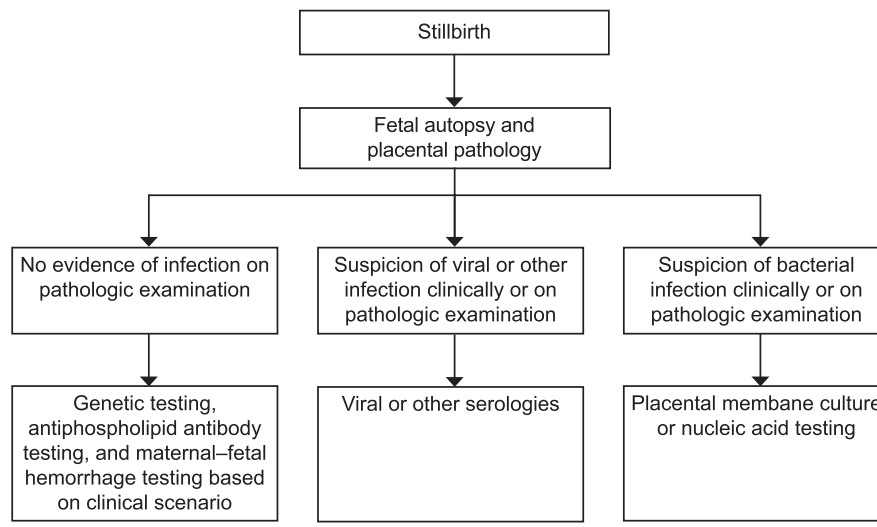

Fig. 2. Algorithm for the evaluation of infection-related stillbirth.
Page. Infection-Related Stillbirths. Obstet Gynecol 2019.

Stillbirth due to infection was more common in non-Hispanic black women and shared pathophysiology with spontaneous preterm birth. Thus, efforts to reduce those infections may also reduce spontaneous preterm births as well as stillbirths. There were also several cases of CMV as well as a small number due to parvovirus and syphilis. Given these data, we do not recommend routine TORCH serology or cultures in the absence of clinical, placental, or autopsy evidence of infection as part of the routine evaluation for stillbirth.

REFERENCES

1. MacDorman MF, Gregory EC. Fetal and perinatal mortality: United States, 2013. Natl Vital Stat Rep 2015;64:1–24.
2. Goldenberg RL, McClure EM, Saleem S, Reddy UM. Infection-related stillbirths. Lancet 2010;375:1482–90.
3. The Stillbirth Collaborative Research Network Writing group. Causes of death among stillbirths. JAMA 2011;306: 2459–68.
4. Parker CB, Hogue CJR, Koch MA, Willinger M, Reddy U, Thorsten VR, et al. For the stillbirth collaborative research network. Stillbirth collaborative research network: design, methods and recruitment experience. Paediatric Perinatal Epidemiol 2011;25:425–35.
5. Pinar H, Koch MA, Hawkins H, Heim-Hall J, Shehata B, Thorsten VR, et al. The stillbirth collaborative research network (SCRN) placental and umbilical cord examination. Am J Perinatol 2011;28:781–92.
6. Pinar H, Koch MA, Hawkins H, Heim-Hall J, Abramowsky CR, Thorsten V, et al. The stillbirth collaborative research network postmortem examination protocol. Am J Perinatol 2012; 29:187–202.
7. Management of stillbirth. ACOG Practice Bulletin No. 102. American College of Obstetricians and Gynecologists. Obstet Gynecol 2009;113:748–61.
8. Stillbirth Collaborative Research Network Writing Group. Association between stillbirth and risk factors known at pregnancy confirmation. JAMA 2011;306:2469–79.
9. Dudley DJ, Goldenberg R, Conway D, Silver RM, Saade GR, Varner MW, et al. A new system for determining the causes of stillbirth. Obstet Gynecol 2010;116:254–60.
10. Page JM, Christiansen-Lindquist L, Thorsten V, Parker CB, Reddy UM, Dudley DJ, et al. Diagnostic tests for evaluation of stillbirth: results from the stillbirth collaborative research network. Obstet Gynecol 2017;129:699–706.
11. Tolockiene E, Morsing E, Holst E, Herbst A, Ljungh A, Svenningsen N, et al. Intrauterine infection may be a major cause of stillbirth in Sweden. Acta Obstet Gynecol Scand 2001;80:511–8.
12. Nan C, Dangor Z, Cutland CL, Edwards MS, Madhi SA, Cunnington MC. Maternal group B streptococcus-related stillbirth: a systematic review. BJOG 2015;122:1437–45.
13. Seale AC, Blencowe H, Bianchi-Jassir F, Embleton N, Bassat Q, Ordi J, et al. Stillbirth with group B streptococcus disease worldwide: systematic review and meta-analysis. Clin Inf Dis 2017;65:S125–32.
14. Group B Streptococcus Vaccine Development Technology Roadmap. Priority activities for development, testing, licensure and global availability of group B streptococcus vaccines. Geneva, Switzerland: World Health Organization; 2017.

PEER REVIEW HISTORY

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