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Examination of a Stillbirth Workup: A Rural Statewide Experience

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Abstract

Objective: The objective of our study was to determine whether recommended assessments were conducted on stillbirths delivered in our predominantly rural state.

Methods: This was a descriptive study of stillbirths delivered in a rural state and included in one site of the Birth Defects Study to Evaluate Pregnancy Exposures stillbirth study. Hospital and fetal death records were examined to determine whether the following areas were evaluated: genetic testing (noninvasive perinatal testing, quad screen, amniocentesis/chorionic villus sampling with karyotype, microarrays, fetal tissue specimen), placenta/membrane/cord sent for pathologic examination, examination of the stillbirth after delivery by the healthcare provider, and fetal autopsy was performed.

Results: From July 1, 2015 to June 30, 2020, there were 1108 stillbirths delivered in Arkansas. The most frequent assessments undertaken were placental pathology (72%), genetic testing (67%), fetal inspection (31%), and autopsy (13%). All 4 assessments were done in 2% of stillbirth cases, 3 assessments in 27%, 2 assessments in 47%, 1 assessment in 14%, and no assessment in 15%. There was no association between stillbirth assessment evaluation by gestational age (<28 weeks and >28 weeks; $P = 0.221$); however, there was an overall association between hospital delivery volume with number of components completed ($P < 0.0001$). Hospitals with >2000 deliveries had a higher proportion of 3 or 4 completions compared with those hospitals with <1000 deliveries or 1000 to 2000 deliveries ($P = 0.021$ and $P < 0.0001$).

[B]Is the CDC funding W.N.N. received separate from that outlined in the funding disclosure paragraph or the same?

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Conclusions: Fetal stillbirth assessment is suboptimal in our rural state, with 15% of stillbirths having no assessment and only 2% having all 4 assessments. There is no association between stillbirth assessment and gestational age (<28 weeks vs >28 weeks), but there is a correlation between delivery volume and stillbirth assessment.

Keywords

fetal autopsy; genetic testing; placental pathology; rural state; stillbirth

Stillbirth, defined as an intrauterine fetal death at 20 gestational weeks or later, complicates 1 in 160 deliveries in the United States and is considered one of the most common adverse pregnancy outcomes.[1,2] According to *National Vital Statistics Reports*, a total of 23,595 stillbirths were reported in the United States in 2013, which is 5.96 fetal deaths per 1000 live births and fetal deaths. Other than some minor fluctuations, the stillbirth rate in the United States has remained relatively unchanged since 2006, at 6.05 fetal deaths per 1000 live births and fetal deaths.[3]

In an effort to better identify the causes of stillbirth, the Stillbirth Collaborative Research Network (SCRN) was initiated by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Between March 2006 and September 2008, SCRN conducted a prospective population-based, case-control study of stillbirths, which included a total of 512 stillbirths from 59 tertiary care and community hospitals across 5 states. The recommended stillbirth evaluation in that study included perinatal postmortem examination, placental histopathology, fetal karyotype, testing for fetal–maternal hemorrhage, antibody screen, serologic test for syphilis, parvovirus serology, glycated hemoglobin, anticardiolipin antibodies, and toxicology screen to evaluate for conditions (eg, infections, chromosomal and fetal structural abnormalities, maternal–fetal hemorrhage, maternal disease) known to be associated with stillbirth.[1] A secondary analysis of the 512 stillbirths was subsequently done to estimate the usefulness of each diagnostic test in the workup for potential causes of stillbirth. The most useful tests identified were placental pathology (64.6%), fetal autopsy (42.4%), genetic testing (11.9%), and testing for antiphospholipid antibodies (11.1%).[4]

Both the American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine recommend that the evaluation of a stillbirth should include fetal autopsy; gross and histologic examination of the placenta, umbilical cord, and membranes; and genetic evaluation.[2] Despite these recommendations, evaluations for causes of stillbirth often are incomplete. The purpose of this study was to evaluate the statewide experience in the evaluation of pregnancies complicated by stillbirth and to determine how often a complete stillbirth evaluation is performed.

Methods

This was a retrospective descriptive study analyzing the evaluation of all of the stillbirths born in Arkansas to resident women from July 1, 2015 to June 30, 2020. This study was approved by the university institutional review board.

Stillbirth was defined for the study as an intrauterine fetal death occurring at a gestational age of 20 weeks or later. Data were obtained as part of the Centers for Disease Control and Prevention–funded Birth Defects Study to Evaluate Pregnancy Exposures stillbirth study, a population-based case-control study that began in 2015 and aimed to better understand the etiology of stillbirths. Arkansas was one of two states participating in the study. Stillbirth cases were identified from the Arkansas Reproductive Health Monitoring System, which has conducted statewide surveillance since 1993 for pregnancies affected by a birth defect and pregnancies ending in a stillbirth without birth defects. Health information specialists abstracted medical records for stillbirth cases identified from multiple overlapping sources: hospital indices from all birthing hospitals and medical facilities in the state based on *International Classification of Diseases, Tenth Revision, Clinical Modification* codes for stillbirth, intrauterine fetal death, and spontaneous abortion; fetal death records from the Arkansas Department of Health; and a university-based statewide tele-ultrasound system. All of the case medical records were reviewed by two investigators (D.D.W. and E.F.M.).

Study Variables

Maternal prenatal, delivery, and sociodemographic information was obtained from the provided records and included maternal age (years), race (White, Black, Hispanic, other), and gestational age at delivery (completed weeks). The following variables associated with stillbirth evaluation were analyzed: fetal inspection at the time of delivery, fetal autopsy, genetic testing (cell-free DNA or noninvasive perinatal testing [NIPT], quad screen, amniocentesis, chorionic villus sampling [CVS], fetal tissue specimen) and whether gross and histologic examination of placenta, umbilical cord, and membranes were performed.

Statistical Analysis

Summary statistics are presented as means and standard deviations (SDs) for continuous measures and frequencies as percentages for categorical variables. The associations between stillbirth component completion with intermediate and late fetal stillbirth and hospital volume were assessed using χ^2 tests. Hospital volume was defined as “low volume” for those hospitals with fewer than 1000 deliveries per year and “high volume” represent those hospitals with >1000 deliveries per year. For statistically significant overall χ^2 omnibus tests, post hoc tests were performed with adjusted *P* values based on the Simes’ test. All of the analyses were conducted using statistical software SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 1108 stillbirths occurred in Arkansas to resident women from July 1, 2015 to June 30, 2020. The majority of the mothers were either White (56%) or African American (34%), with a mean age of 27 years old (SD 6.3). The mean gestational age was 28.7 weeks (SD 6.5), and slightly more than half of the infants were male (53%) (Table 1).[A]

[A]Per journal policy, the table “Summary of Stillbirth Evaluation Recommendations” was made into supplemental digital content. Please indicate where in the text to place the callout for it.

Figure 1 is a summary of the recommended stillbirth evaluation components and the frequency with which each component was completed. The most frequently performed component of the stillbirth evaluation was placental pathology (72%), followed by cytogenetics (67%), fetal inspection (31%), and fetal autopsy (13%). Of note, the data regarding cytogenetics include screening modalities (ie, cell-free DNA or NIPT) in addition to diagnostic testing (via amniocentesis, CVS, or fetal tissue specimen) with karyotype or chromosomal microarray, because this was not always delineated within the Arkansas Reproductive Health Monitoring System. We were only able to identify diagnostic testing with karyotype, fluorescence in situ hybridization, or chromosomal microarray specifically in 27 stillbirth cases (27 in 1108, 2.4%).

Figure 2 displays the number of completed components for each stillbirth evaluation. At least 2 components were completed most frequently, occurring in 518 of 1108 (47%) of cases, with placental pathology and cytogenetics (screening or diagnostic testing) being the portions most commonly performed. At least 3 components were completed in 245 of 1108 (22%) cases, and all 4 components were completed in only 28 of 1108 (2.5%) cases. None of the stillbirth evaluation components were completed in 167 (15%) cases.

According to the National Vital Statistics System, stillbirth can be further divided into 3 periods: early (<20 completed weeks of gestation), intermediate (20–27 weeks of gestation), and late (≥28 weeks of gestation).[3] Table 2 provides data regarding stillbirth component completion divided into intermediate and late stillbirth. There were no statistically significant differences in the number of components completed based on gestational age.

Tables 3 and 4 analyze stillbirth component completion by hospital volume. Overall, there was an association between hospital volume low/high with total number of components completed ($P < 0.0001$). More specifically, low-volume hospitals had a higher number of cases with none of the components completed (19.1% vs 13.9%, $P = 0.031$) compared with high-volume hospitals. Although the proportion of one component completed was higher among high-volume hospitals (18.7% vs 8.2%; $P < 0.0001$), high-volume hospitals had lower proportions of two components completed compared with low-volume hospitals (40.0% vs 47.2%, $P = 0.029$). There were no differences among the two types of hospitals based on their proportions for three or four components completed. When we combined the evaluations into a binary indicator (ie, <3 vs 3 or 4 completed), there were no statistical differences based on hospital volume ($P = 0.521$). In Table 4, we defined a three-level hospital volume based on number of annual deliveries (<1000, 1000–2000, and >2000). Overall, there was an association between the 3-level hospital volume with the total number of components completed ($P < 0.0001$). Hospitals with fewer than 1000 deliveries per year had a higher percentage of zero components completed compared with those hospitals with >2000 deliveries ($P = 0.012$). In addition, the hospitals with >2000 deliveries had a higher proportion of completing 2 or 3 components compared with both hospitals with 1000 to 2000 deliveries or those with <1000 deliveries.

Discussion

This study examined the required components of the stillbirth evaluation to determine the healthcare providers' compliance with recommended guidelines, including fetal inspection at delivery, fetal autopsy, genetic testing (cell-free DNA or NIPT, quad screen, amniocentesis, CVS, fetal tissue specimen), and gross and histologic examination of placenta, umbilical cord, and membranes. Only 2% of the stillbirth evaluations included all 4 components: 27% included 3 components, 47% included 2 components, and 14% included 1 component. None of the evaluation components were completed in 15% of cases.

Decreasing autopsy rates and lack of uniform protocols to evaluate and classify stillbirths have hindered providers' ability to identify specific causes of stillbirth, some of which may have significant impact in future pregnancies and appropriate patient counseling.[2] The current stillbirth rate in Arkansas is above the 5.96/1000 US national average at 6.51/1000 live births.[3] With increased recognition of the recommended components of a stillbirth evaluation and implementation of uniform protocols, there is potential for future stillbirths to be prevented. In a prospective case-control study of stillbirths performed by SCRN, only 24% of stillbirth cases were left unexplained following a uniform and thorough evaluation.[1]

Fetal Examination

Prompt evaluation of the stillborn fetus is recommended, with particular attention paid to any dysmorphic features. Frontal and profile photographs of the whole body, face, extremities, palms, and any abnormalities should be documented, as well as fetal weight, head circumference and length.[2] In this study, the delivering physicians described their examination of the stillborn fetus in only 31% of cases.

Fetal Autopsy

A fetal autopsy is one of the most useful components of the stillbirth evaluation and should always be offered.[2,5] Important diagnostic information is obtained in up to 30% of cases. The diagnostic yield is further increased when dysmorphic features, anomalies, inconsistent growth measurements, fetal growth restriction, or fetal hydrops is present. If a patient declines a complete autopsy, then other options, including partial autopsy, external evaluation by a trained perinatal pathologist, and imaging (X-ray, ultrasonography, or magnetic resonance imaging) can be offered and may provide information regarding the cause of fetal death.[2] In this study, a fetal autopsy was only performed in 13% of stillbirth cases. There are several perceived barriers to completing an autopsy, including parental concerns (cost, insurance noncoverage, invasiveness of procedure, emotional distress, poor understanding of the potential future value of the autopsy), cultural or religious concerns, or provider concerns (lack of familiarity with discussing autopsy).[5,6] Despite the diagnostic utility of performing a fetal autopsy, insurance companies rarely cover the cost of this service, which is a significant barrier for many patients who are not able to cover the cost.

Genetic Evaluation

Studies have demonstrated that genetic analyses are of sufficient yield that they should be performed in all cases of stillbirth after obtaining parental consent. On average, an abnormal

karyotype can be found in approximately 6% to 15% of stillbirths.[1,2,5,7,8] In a large study in the Netherlands, the rate of karyotype abnormalities reached 38% in the presence of fetal anatomic abnormalities, dysmorphic features, and the fetal growth restriction of hydrops.[9] The most common abnormalities found in stillbirths are trisomy 21 (31%), monosomy X (22%), trisomy 18 (22%), and trisomy 13 (8%).[2,5,8]

Acceptable cytogenetic specimens include amniotic fluid obtained by amniocentesis at the time of prenatal diagnosis of demise (greatest yield), a placental block (1 × 1 cm) taken from below the cord insertion site that includes the chorionic plate, an umbilical cord segment (1.5 cm) taken close to the cord insertion into the fetus, or internal fetal tissue specimen (eg, costochondral junction, patella). Fetal skin is not recommended for cytogenetic studies.[2] Unfortunately, the numbers of stillbirths attributable to karyotype abnormalities are likely underestimated because of cell cultures being unsuccessful in up to 60% of karyotype attempts.[7,8] If possible, chromosomal microarray is recommended over karyotype because microarray not only detects aneuploidy but also is able to detect copy-number variants (smaller deletions and duplications) and is more successful than karyotype with nonviable tissue.[2,5]

Approximately 67% of the women in this study had some type of cytogenetic material sent for assessment (including screening tests performed); however, only 2% had material sent for diagnostic testing, including karyotype, fluorescence in situ hybridization, or chromosomal microarray). This number is even smaller if you consider that a number of these women underwent antepartum assessments for fetal aneuploidy because of abnormal serum screens and/or abnormal targeted ultrasounds before an intrauterine demise.

Placenta, Umbilical Cord, and Membranes

The SCRN noted that placental disease was the leading cause of antepartum stillbirth (26%), with umbilical abnormalities accounting for an additional 10% of possible or probable causes of death.[1] Examination of the placenta, umbilical cord, and fetal membranes by a trained pathologist is the single most useful aspect of the evaluation of stillbirth.[4,9,10] Placental evaluation may provide information regarding infection, genetic abnormalities, anemia, or conditions such as abruption, umbilical cord thrombosis, velamentous cord insertion, and vasa previa. Chorionicity and vascular anastomoses in multifetal gestations also can be identified and confirmed.[10] Umbilical cord knots or cord entanglement should be noted, although they should be interpreted with caution because these may be found in normal pregnancies.[2] Criteria that should be considered before determination that a cord abnormality was the cause of stillbirth include presence of vasa previa, cord entrapment, evidence of occlusion and fetal hypoxia, prolapse, or stricture with thrombi.[1] The presence of a nuchal cord alone is generally not considered to be a cause of death.[11] In all cases of possible cord event, other causes of stillbirth should be excluded.[2] In this study, the placenta was the most commonly performed component of the stillbirth evaluation and was completed in 72% of cases.

Limitations and Strengths of the Study

One limitation of this study is that medical records did not contain specific details of medical provider–patient conversations regarding which components of tissue testing and evaluation were offered and how and/or why decisions were made. In the absence of documentation within the database, we assumed that particular component of the stillbirth evaluation was not performed. Because of the retrospective nature of the study and multiple locations across the state, we were unable to discuss local practices and review specific cases with participating physicians.

One of the strengths of this study is that cases were ascertained from a statewide, population-based surveillance system that used active case-finding methods to monitor all births, regardless of outcome. Another strength is that stillbirth cases were ascertained from multiple sources so the possibility of under-ascertainment of cases is very low. Our study also had a large sample size and all of the stillbirth cases were clinically reviewed and confirmed.

Conclusions

This study accentuates the need for increased provider education on the recommended evaluation of stillbirth and highlights areas for improvement in obstetric care in our rural, southern state to better identify specific causes of stillbirth. In particular, areas of improvement in stillbirth evaluations include documenting and describing the fetal physical features at the time of stillbirth delivery, offering autopsy, and offering diagnostic genetic testing, specifically, karyotype and/or chromosomal microarray. These recommendations are highlighted in the American College of Obstetricians and Gynecologists and Society for Maternal Fetal Medicine Management of Stillbirth: Obstetric Care Consensus No. 10, a guideline for stillbirth risk factors, examination, testing, counseling, and management.[2] For many patients, cost and lack of insurance coverage is a limiting factor in performing a fetal autopsy and obtaining diagnostic genetic testing. Reform at the state level and/or expanded insurance coverage for these services is critical. There is much work to do in understanding and reducing stillbirth. More studies to evaluate and improve the limitations of vital information to better understand stillbirth is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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[A] You disclosed funding from NIH in the Public Access Policy funding disclosure. Would you please provide the grant number and the name of the grant recipient?

Key Points

- The frequency of the assessments after a stillbirth was 72% for placental pathology, 67% for genetic testing, 31% for fetal inspection at delivery, and 13% for fetal autopsy.
- All 4 stillbirth assessments were accomplished in 2% of stillbirth cases, 3 assessments in 27%, 2 assessments in 47%, 1 assessment in 14%, and no assessment in 15%.
- There was no correlation between the gestational age at the time of the demise (<28 weeks vs >28 weeks) and the number of components completed, but there was a correlation between the numbers of hospital deliveries. Hospitals with a delivery volume of >2000 annual deliveries had more 3- or 4-component completions than hospitals with <1000 annual deliveries.

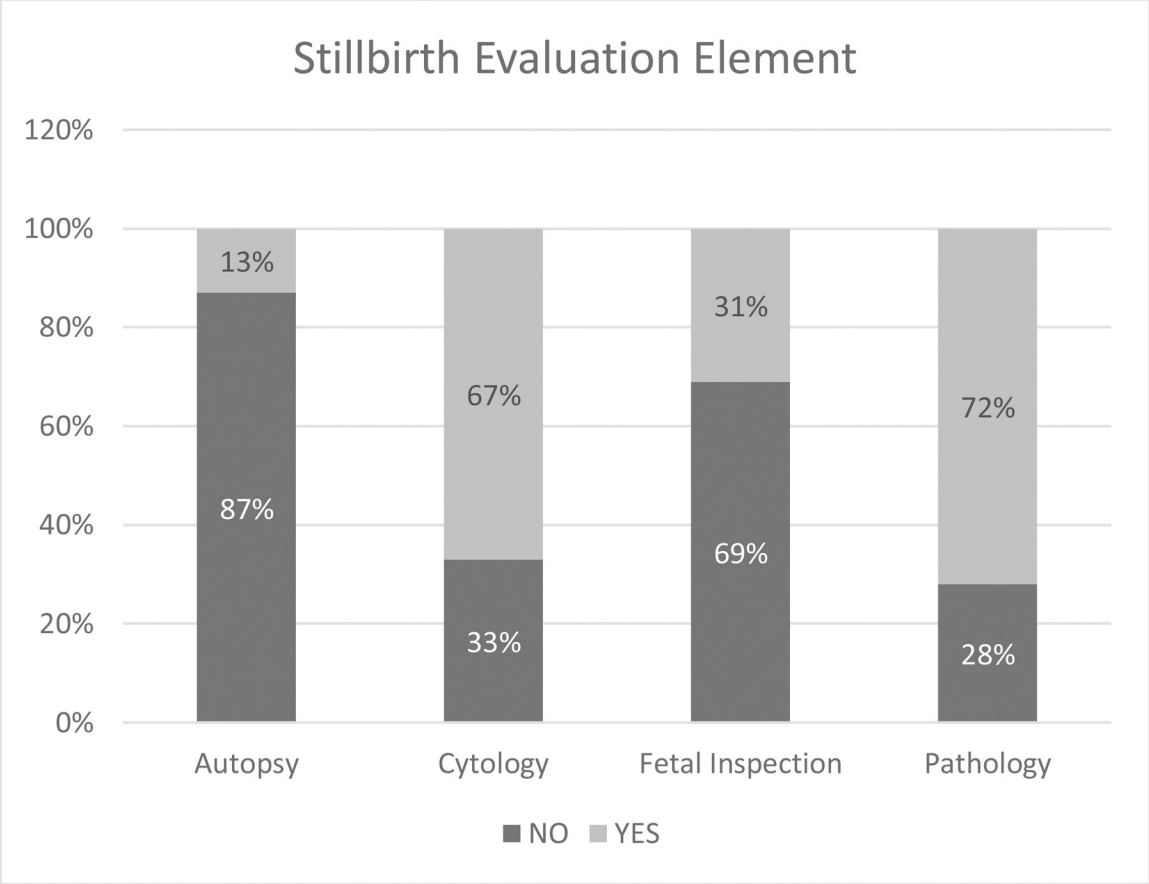

Fig. 1.
Recommended stillbirth evaluation components.

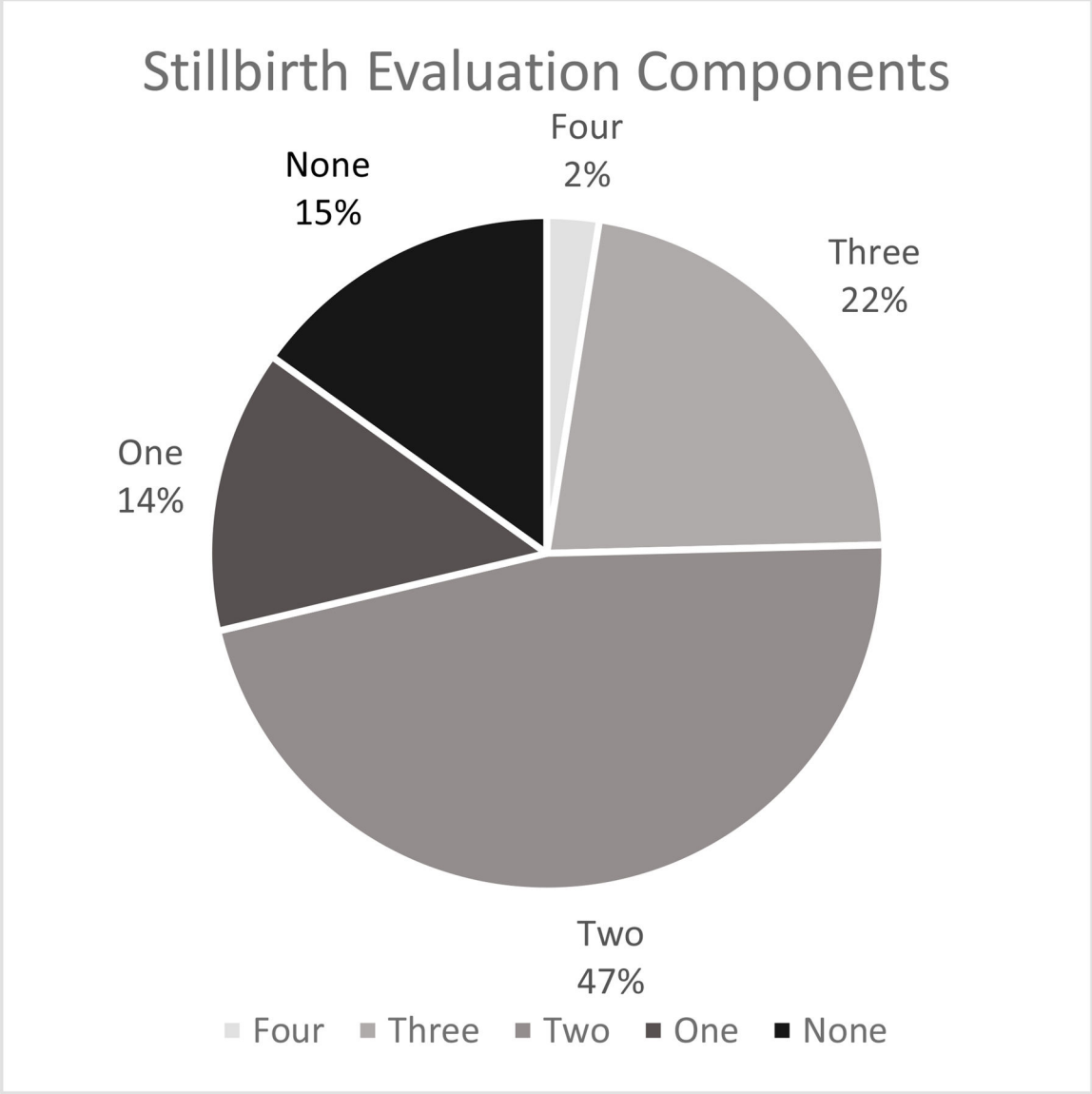

Fig. 2.
Breakdown of number of stillbirth evaluation components.

Table 1.

Demographic characteristics overall and by intermediate or late fetal stillbirth (N = 1108)

Measures	Overall	Intermediate (GA ≤ 28)	Late (GA > 28)
Maternal age, y, mean ± SD	27.5 ± 6.3	27.2 ± 6.4	27.8 ± 6.2
Race, N (%)[a]			
White	612 (55.8)	289 (51.4)	321 (60.5)
Black	371 (33.9)	209 (37.2)	161 (30.3)
Other	113 (10.3)	64 (11.4)	49 (9.2)
Infant sex, N (%)[a]			
Male	565 (52.8)	283 (51.6)	281 (54.0)
Female	506 (47.3)	265 (48.4)	239 (46.0)
GA, mean ± SD [a]	28.7 ± 6.6	23.1 ± 2.5	34.8 ± 3.3

GA, gestational age; SD, standard deviation.

[a]Measure contains missing observations.

Table 2.

Relationship between evaluation components for stillbirths and gestational age using χ^2 tests, Arkansas, 2015–2020 (N = 1108)

Components	Gestational age ≤28 wk, n (%)	Gestational age >28 wk, n (%)	Total[A]	*P*
0	86 (15.1)	80 (15.0)		0.221
1	73 (12.8)	76 (14.3)		
2	282 (49.4)	234 (44.0)		
3	120 (21.0)	124 (23.3)		
4	10 (1.8)	18 (3.4)		
≥3				0.131
No	441 (77.2)	390 (73.3)		
Yes	130 (22.8)	142 (26.7)		

[A]Are there no values for the “Total” column in Table 2? If not, should it be deleted?

Table 3.

Relationship between evaluation components for stillbirths and hospital volume using χ^2 tests, Arkansas, 2015–2020 (N = 1108)

Component	Low volume, n (%)	High volume, n (%) volume	*P* [A]
			<0.0001[a]
0	77 (19.1)	76 (13.9)	0.031
1	33 (8.2)	102 (18.7)	<0.0001
2	190 (47.2)	219 (40.0)	0.029
3	92 (22.8)	135 (24.7)	0.508
4	11 (2.7)	15 (2.7)	0.991
≥3			0.521
No	300 (74.4)	397 (72.6)	
Yes	103 (25.6)	150 (27.4)	

High-volume hospitals were defined as those with >1000 deliveries; 158 observations had missing hospital volume information.

[a]Denotes overall χ^2 test.

[A]Please correct the value alignment in the P value column (something is off as received).

Table 4:

Relationship between Evaluation Components for Stillbirths and 3-level Hospital Volume, using Chi-Squared Tests, Arkansas, 2015–2020 (n=11XX)

	Number of Deliveries				
Components	< 1000	1000 – 2000	> 2000	p-value	Post-hoc Test[a]
Overall chi-square test (omnibus test)				<0.0001	
None	77 (19.1%)	37 (17.3%)	39 (11.7%)	0.022	1 vs 3 (p=0.012);
One	33 (8.2%)	25 (11.7%)	77 (23.1%)	<0.0001	1 vs 3 (p=0.0004); 2 vs 3 (p=0.0004)
Two	190 (47.2%)	113 (52.8%)	106 (31.8%)	<0.0001	1 vs 3 (p<0.0001); 2 vs 3 (p=0.00014)
Three	92 (22.8%)	35 (16.4%)	100 (30.0%)	0.001	1 vs 3 (p=0.027); 2 vs 3 (p=0.009);
Four	11 (2.7%)	4 (1.9%)	11 (3.3%)	0.605	
≥ Three Components				0.0004	1 vs 2 (p=0.039); 1 vs 3 (p=0.021); 2 vs 3 (p<0.0001);
No	300 (74.4%)	175 (81.8%)	222 (66.7%)		
Yes	103 (25.6%)	39 (18.2%)	111 (33.3%)		

Note: 158 observations had missing hospital volume information;

[a]Post-hoc comparison adjusted p-value using the Simes' test; 1 = <1000; 2 = 1000–2000; 3 = >2000.