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Stillbirth evaluation: a stepwise assessment of placental pathology and autopsy

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BACKGROUND: The American Congress of Obstetricians and Gynecologists places special emphasis on autopsy as one of the most important tests for evaluation of stillbirth. Despite a recommendation of an autopsy, many families will decline the autopsy based on religious/cultural beliefs, fear of additional suffering for the child, or belief that no additional information will be obtained or of value. Further, many obstetric providers express a myriad of barriers limiting their recommendation for a perinatal autopsy despite their understanding of its value. Consequently, perinatal autopsy rates have been declining. Without the information provided by an autopsy, many women are left with unanswered questions regarding cause of death for their fetus and without clear management strategies to reduce the risk of stillbirth in future pregnancies. To avoid this scenario, it is imperative that clinicians are knowledgeable about the benefit of autopsy so they can provide clear information on its diagnostic utility and decrease potential barriers; in so doing the obstetrician can ensure that each family has the necessary information to make an informed decision.

OBJECTIVE: We sought to quantify the contribution of placental pathologic examination and autopsy in identifying a cause of stillbirth and to identify how often clinical management is modified due to each result.

STUDY DESIGN: This is a cohort study of all cases of stillbirth from 2009 through 2013 at a single tertiary care center. Records were reviewed in a stepwise manner: first the clinical history and laboratory results, then the placental pathologic evaluation, and finally the autopsy. At each step, a cause of death and the certainty of that etiology were coded. Clinical changes that would be recommended by information available at each step were also recorded.

RESULTS: Among the 144 cases of stillbirth examined, 104 (72%) underwent autopsy and these cases constitute the cohort of study. The clinical and laboratory information alone identified a cause of death in 35 (24%). After placental pathologic examination, 88 (61%) cases had a probable cause of death identified. The addition of autopsy resulted in 78 (74%) cases having an identifiable probable cause of death. Placental examination alone changed clinical management in 52 (36%) cases. Autopsy led to additional clinical management changes in 6 (6%) cases.

CONCLUSION: This stepwise assessment of the benefit of both placental pathological examination and autopsy in changing probable cause of death beyond traditional clinical history and laboratory results emphasizes the need to implement more comprehensive evaluation of all stillbirths. With the aim of providing a cause of stillbirth to the parents, and to prevent future stillbirths, it behooves health care professionals to understand the value of this more comprehensive approach and convey that information to the bereaved parents.

Key words: autopsy, perinatal pathology, placental pathology, stillbirth

Introduction

Stillbirth affects 6.1 of every thousand pregnancies in the United States annually.[1] Complete obstetric management ideally includes review of the clinical history, laboratory assessment, examination of the placenta, genetic evaluation, and fetal autopsy.[2] The information from these studies can be used to glean information regarding antenatal growth, fetal development, congenital anomalies, and to confirm or refute the clinical diagnoses. Information from a complete postmortem examination, in turn, informs probable cause of death and potential intervention strategies and management in subsequent pregnancies.

A detailed placental pathologic examination is one critical component of stillbirth evaluation given the placenta's essential role in maintaining a healthy pregnancy. Indeed, prior studies have shown that placental examination, in addition to review of the clinical history and laboratory assessments, can identify a cause of death in 11-65% of cases.[3] In addition to placental pathology, American Congress of Obstetricians and Gynecologists (ACOG) places special emphasis on autopsy as one of the most important tests for evaluation of stillbirth.[4] Despite recommendation of an autopsy, many families will decline the autopsy based on religious/cultural beliefs, fear of additional suffering for the child, or belief that no additional information will be obtained or of value. Further, many obstetric providers express a myriad of barriers limiting their recommendation for a perinatal autopsy[5] despite their understanding of its value. Consequently, perinatal autopsy rates have been declining.[4,6] Without the information provided by an autopsy, many women are left with unanswered questions regarding cause of death for their fetus and without clear management strategies to reduce the risk of stillbirth in future pregnancies. To avoid this scenario, it is imperative that clinicians are knowledgeable about the benefit of autopsy so they can provide clear information on its diagnostic utility and decrease potential barriers; in so doing the obstetrician can ensure that each family has the necessary information to make an informed decision.

Accordingly, the objectives of this study are to use a stepwise design to quantify the specific contributions of placental pathology and autopsy in identifying a cause of death and to identify how often clinical management for subsequent pregnancies should change due to each of these results.

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Materials and Methods

General study design

This is a cohort study of all cases of stillbirth with delivery at ≥23 weeks at Northwestern University. To study a population of true intrauterine fetal demises and avoid misclassification of terminations of pregnancy, stillbirths <23 weeks' gestation or intrapartum stillbirths (ie, extreme prematurity without planned neonatal resuscitation) were excluded. Cases were retrospectively collected from January 2009 through September 2011 by query of a comprehensive institutional database of placental pathologic exams. Thereafter cases were prospectively collected until August 31, 2013. Pregnancies were dated by their primary obstetrician using ACOG-accepted methods.[7] The clinical diagnosis of stillbirth was made by ultrasonographic evidence of asystole, confirmed by 2 providers.

The clinical approach to stillbirth employed by all physicians during the study time period included the following: (1) a detailed history and physical exam of the mother along with a gross neonatal physical exam by the obstetrician at delivery; (2) laboratory testing via a standard order set in the electronic medical chart including maternal serum evaluation for infections (cytomegalovirus, parvovirus, toxoplasma, and syphilis), acquired thrombophilia (ie, antiphospholipid antibodies), and fetomaternal hemorrhage; (3) a recommendation for chromosomal analysis of the stillborn (standard karyotype at the time of the study); (4) placental pathologic examination; and (5) a recommendation for autopsy followed by a formal consent process emphasizing the potential benefits of the knowledge gained.

Placental pathologic examination

All patients underwent a detailed, systematic gross and histologic placental pathologic examination by a single attending perinatal pathologist (L.M.E.). This examination included recording of the trimmed placental weight, membrane insertion, dimensions of the placental disc, and insertion, length, diameter, and coiling pattern of the umbilical cord. Histologic samples included sections of membranes, umbilical cord, and 2-5 sections of the placental parenchyma. The histologic data were recorded and divided into 3 major pathologic categories: maternal vascular underperfusion, fetal vascular obstruction/fetal thrombotic vasculopathy, and evidence of amnionic fluid infection, using criteria defined by Redline et al.[8-10] Per hospital protocol, the final placental pathologic report is completed prior to completion of the final autopsy report.

Autopsy examination

Components of the complete autopsy performed are described in Table 1. Autopsy was performed at no charge to the family by an expert perinatal pathologist (L.M.E.).

Stepwise analysis

Demographic characteristics, the clinical history and physical examination, and the clinically suspected cause of death were compared between women who agreed to autopsy and those who declined. For all women, records were reviewed by a maternal-fetal medicine subspecialist (E.S.M.) in a stepwise manner. Step 1: the clinical history, delivery notes, and laboratory assessments were reviewed, blinded to placental pathology and autopsy data. Step 2: placental pathologic report was reviewed, in consultation with the perinatal pathologist as needed, and in concert with the clinical data, but blinded to the autopsy data. Step 3: If applicable, the autopsy information was reviewed and that information was compiled with results from the clinical data, laboratory assessments, and placental pathologic examination (Figure 1).

At each step of these stillbirth examinations, the cause of death was ascribed and the certainty of that etiology coded according to the initial causes of fetal death (INCODE) method.[11] The INCODE system divides etiologies of stillbirth into 7 major categories: maternal medical conditions during pregnancy, obstetric complications, maternal or fetal hematologic conditions, fetal abnormalities, infectious etiologies, placental pathologic conditions, or other. Conditions listed as possible cause of death were those not believed to be a direct cause of the stillbirth, but possibly involved in the pathophysiologic sequence that led to death. Examples of "possible cause of death" include uncontrolled maternal seizures, inherited thrombophilia with a small-for-gestational-age fetus, fetal muscular dystrophy, inflammation limited to placenta, or velamentous cord insertion with no evidence of occlusion. Conditions listed as probable cause of death had a high likelihood of directly causing the fetal death. Examples of "probable cause of death" include included cholestasis of pregnancy, massive fetomaternal hemorrhage, fetal hydrops, aneuploidy, microbiologic, molecular or pathognomonic histologic evidence of fetal infection, or evidence of severe maternal or fetal vascular compromise in the placenta. The certainty of the ascribed cause of death (ie, unknown, possible, or probable) was compared between each stage of the evaluation (ie, clinical, placental pathology, and autopsy).

Clinical management recommendations for a future pregnancy as a result of the collected information were determined by a maternal-fetal medicine subspecialist (E.S.M.) and were examined sequentially. Examples of clinical management strategies to be employed in a future pregnancy included obtaining additional laboratory information (ie, neonatal alloimmune thrombocytopenia testing), genetic testing, a more detailed anatomic survey, serial growth ultrasounds, or nonstress tests. Clinical management changes informed by placental pathology alone and after autopsy were examined separately.

Statistical analysis

Statistical analyses were performed using software (Stata, Version 13.1; StataCorp, College Station, TX). Student t, χ^2, Fisher exact, and analysis of variance tests were used, as appropriate. A P value of .05 represented statistical significance. All tests were 2-tailed.

TABLE 1
Components of autopsy examination

Autopsy consent
External gross examination
Photographs
Radiographs
Body measurements
Document maceration
Overall appearance/maturation/identify external anomalies
Obtain skin sample for cytogenetics, if needed
Internal gross examination
Y-incision
Routine cultures: blood, spleen, lung
In situ examination: abdomen
Note presence of peritoneal fluid
Umbilical vessels and bladder: note position, size, any abnormalities
Large bowel: fixation of cecum and appendix, fixation of left colon
Small bowel: ligament of Treitz, position and length of mesenteric root
Stomach: position, note abnormalities
Pancreas: tail should extend to spleen, rule out annular pancreas
Spleen: note position, rule out polysplenia or asplenia
Liver and gall bladder: position and shape
Genitalia: note position, any abnormalities
Kidney and ureters: note position, cystic change, dilation of ureters
Diaphragm: check for intactness, level of domes
In situ examination: neck and thorax
Thymus: position, shape, and size
Pericardial sac: fluid, look for defects
Pleural cavities: fluid, lobation of lungs
Heart and great vessels
Removal of organ block and dissection of individual organs
Removal of brain
All organs weighed and any anomalies recorded
Sampling of tissues for histologic examination
Recording of gross findings
Provisional anatomic diagnoses
Released to clinical team within 2 working days of autopsy dissection
Review of histologic slides and recording of histologic findings
Brain gross and histologic examination after fixation
Review of all ancillary studies (genetic, metabolic, microbiology)
Final autopsy report including final anatomic diagnoses, summary of clinical history, gross description, microscopic description, and clinicopathologic correlation released to clinical team within 60 working days of autopsy dissection.

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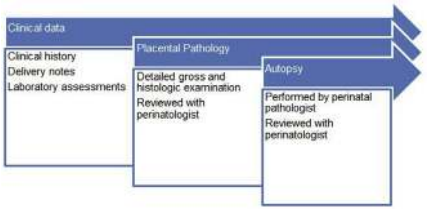
FIGURE 1
Stepwise approach to stillbirth evaluation



Schema of stepwise stillbirth analysis.

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Institutional review board approval

Approval for this study was obtained from the Northwestern University Institutional Review Board with a waiver of informed consent.

Results

There were approximately 12,000 deliveries per year during the study period. A total of 171 cases of stillbirth were identified during the 56-month window during which this cohort was accrued. Of these, 27 (15.8%) were excluded as they were either pregnancy terminations or cases of extreme prematurity without planned neonatal resuscitation, leaving 144 in the analyzable cohort. All 144 stillbirth cases had undergone a detailed maternal history and physical, laboratory testing for a cause of stillbirth, and a detailed placental pathologic exam. A karyotype was sent in 85 (59.0%) stillbirths. Of those sent, 74 (87.1%) resulted and, of those that resulted, 9 (12.2%) were abnormal. Complete autopsies were done in 104 (72%) of these cases. Demographic and clinical characteristics of cases, dichotomized by consent for autopsy (n = 104) or not (n = 40) are shown in Table 2. The causes of death as categorized by the INCODE method, determined by the clinical evaluation only, are also shown in Table 2.

Of the 144 stillbirth cases, step 1 evaluation (clinical and standard laboratory assessment) identified a probable cause of death in 35 (24.3%): 17 (42.5%) of those who declined autopsy and 18 (17.3%) autopsy cases. After step 2 evaluation (placental pathologic

TABLE 2
Demographics plus cause of death, stratified by autopsy consent

	Group with placental pathology only n = 40	Group with placental pathology plus autopsy n = 104	*P* value
Maternal age, y	30.2 ± 6.7	31.6 ± 6.3	.218
Nulliparous	18 (45.0%)	63 (60.6%)	.091
Race/ethnicity			.514
White	18 (45.0%)	35 (33.7%)	
Black	10 (25.0%)	25 (24.0%)	
Hispanic	5 (12.5%)	5 (24.0%)	
Asian	5 (12.5%)	11 (10.6%)	
Other	2 (5.0%)	8 (7.7%)	
Chronic hypertension	2 (5.0%)	3 (2.9%)	.535
Diabetes	7 (17.5%)	9 (8.7%)	.130
Tobacco use	4 (10.0%)	6 (5.8%)	.371
Gestational age at delivery	32.4 ± 5.5	32.9 ± 5.4	.642
Birthweight, g	1935 ± 1122	1903 ± 1125	.882
LGA or SGA	19 (48.7%)	66 (63.5%)	.110
Cause of death on clinical evaluation only (INCODE)			.002
Unknown	14 (35.9%)	65 (61.9%)	
Maternal medical conditions	8 (20.5%)	8 (7.6%)	
Obstetric complications	7 (18.0%)	15 (14.3%)	
Hematological conditions	0 (0.0%)	4 (3.8%)	
Fetal abnormalities	7 (18.0%)	8 (7.6%)	
Infection	0 (0.0%)	1 (1.0%)	
Placental	0 (0.0%)	4 (3.8%)	
Other	3 (7.7%)	0 (0.0%)	

Data presented as mean ± SD or n (%).

LGA, large for gestational age; *SGA*, small for gestational age.

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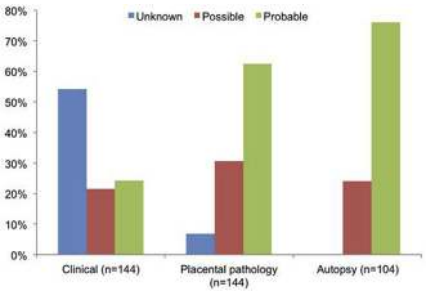
FIGURE 2
Changes in cause of death stratified by stage of examination



Stepwise changes in ascribed cause of death identified.

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examination), 88 (61.1%) had an ascribed probable cause of death. And after adding step 3 evaluation (autopsy), thus a complete stillbirth evaluation, 78 (74.3%) had a probable cause of death identified. These differences were statistically significantly different at each stage of evaluation ($P = .02$). The stepwise incremental increase in knowledge regarding cause of death at each of these 3 steps is depicted in Figure 2. Cases were then stratified by gestational age at delivery (<32 vs ≥32 weeks) and this analysis repeated. Similar rates of possible/probable cause of death were seen at each phase of the evaluation between the groups. The trends seen in the main analysis were not affected by this stratification (data not shown). The specific possible or probable INCODE causes of death are shown in Table 3. The percentage of unknown cause of death decreased at each step of the evaluation. In addition, the percentage of placental causes of death increased with each step.

Medical management recommendations for future pregnancies were altered from that recommended after the clinical and laboratory assessment with the stepwise addition of placental pathologic examination in 52 (36.1%) cases. The most common change suggested after placental pathology included the recommendation for serial growth ultrasounds in a future pregnancy based on placental evidence of a small-for-gestational-age placenta or maternal vascular underperfusion. The stepwise addition of autopsy to the placental and clinical examinations resulted in changes in medical recommendation in 6 (5.7%) cases, for a total of 47 (45.2%) women who agreed to autopsy having clinical management changes due to the results of her placental examination and autopsy combined. Examples of medical management changes recommended after autopsy include a detailed anatomic survey after identification of a previously unsuspected fetal liver hemangioendothelioma, neonatal alloimmune thrombocytopenia testing after uncovering a massive intracerebral hemorrhage, administration of empiric antibiotics after autopsy evidence of fetal group B streptococcal sepsis, and serial middle cerebral artery Doppler studies in a case of anti-M antibody but clear evidence of fetal anemia on autopsy without any other identifiable etiology. The specific changes in medical management after stepwise review of placental pathology and autopsy (either in counseling regarding recurrence risk or clinical management) are presented in Table 4.

Comment

We found that using stepwise analysis of combined detailed placental pathologic

TABLE 3
INCODE cause of death identified at each stage of evaluation

	Clinical data (n = 144)	Placental pathology (n = 144)	Autopsy (n = 104)	*P* value
				<.001
Unknown	79 (54.9%)	8 (5.6%)	1 (1.0%)	
Maternal medical conditions	16 (11.1%)	9 (6.3%)	5 (4.8%)	
Obstetric complications	22 (15.3%)	21 (14.6%)	15 (14.4%)	
Hematological conditions	4 (2.8%)	2 (1.4%)	5 (4.8%)	
Fetal abnormalities	15 (10.4%)	13 (9.0%)	7 (6.7%)	
Infection	1 (0.7%)	3 (2.1%)	4 (3.9%)	
Placental	4 (2.8%)	83 (57.6%)	68 (64.4%)	
Other	3 (2.1%)	5 (3.5%)	0 (0.0%)	

Data presented as n (%).

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evaluation by a perinatal pathologist plus fetal autopsy improved the ability to identify a cause of stillbirth 3-fold compared to clinical evaluation alone. A complete 3-step examination (clinical and laboratory information, placental pathology examination, and autopsy) ultimately afforded a probable diagnosis in 74% of stillbirths. More importantly, the combination of placental pathology and autopsy altered medical management for subsequent pregnancies in nearly half of all stillbirths, thus potentially reducing recurrence risk through planned clinical testing or monitoring. Recognizing that obstetricians have a long-standing relationship with the mothers, they are often faced with questions pertaining to the relative value of the autopsy when obtaining consent for a perinatal autopsy and the need for information on cause of death and recurrence risk.[12] Consequently, the data generated from this contemporary cohort of stillbirth will be of significant value in providing obstetric caregivers concrete information regarding the relative benefits of each step of the stillbirth evaluation.

Several prior publications have ascribed diagnostic value to perinatal autopsy, but the specific value in the setting of stillbirth is less commonly reported.[13-16] In addition, many existing studies combine placental pathologic examination with autopsy results, making it difficult to quantify the relative individual contributions of both a detailed placental examination and autopsy. Furthermore there have been significant advances in the field of prenatal diagnosis since many of these studies were published, limiting application of their results to contemporary practice. Our results indicated that in the hands of a perinatal pathologist, placental pathology uncovered a cause of death in 61% of stillbirth, and that the addition of autopsy increased the determination of cause of death to 74%, a statistically significant increase in the information that can be provided to the family. Some might argue that if placental pathology can identify cause of death in such a large percentage of cases, perhaps there is no need to perform an autopsy. However, we suggest caution in this interpretation because, although not specifically addressed by this study, our experience is that there is value in relaying positive as well as negative autopsy information to families in terms of what led to fetal demise. What also cannot be measured in this cohort is the role of autopsy in buttressing the confidence of the family and clinicians in previously suspected causes of stillbirth. For example, antenatally diagnosed intrauterine growth restriction with oligohydramnios is considered a probable cause of death. In this setting, while autopsy would not overtly improve the ability to provide a cause of death, it allows important modifications and strengthens confidence in the diagnoses. In this case, autopsy may refine the diagnosis by informing the underlying etiology of the growth restriction or identifying previously nonsuspected anomalies. This confirmation of clinical findings and exclusion of other etiologies potentially adds more value to a detailed postmortem examination than what can be quantified in this analysis.[14]

Strengths of this study include its multidisciplinary approach. Detailed pathologic findings were reviewed by both a perinatal pathologist and a perinatologist, potentially enhancing the clinical yield of the pathologic examination.[17] Another strength of this study is the sequential uncovering of clinical, placental, then autopsy results that afforded an opportunity to examine the

TABLE 4
Recommended medical management changes for subsequent pregnancies based on each additional step in evaluation

	Placental pathology	Autopsy
Serial growth ultrasounds	52 (36.1%)	0 (0.0%)
Counseling regarding recurrence risk	5 (3.5%)	3 (2.9%)
Laboratory testing	1 (0.7%)	4 (3.8%)
Fetal surveillance	4 (2.8%)	0 (0.0%)
Genetic testing	1 (0.7%)	2 (1.9%)
Detailed anatomy survey	0 (0.0%)	2 (1.9%)

Data presented as n (%).

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individual contribution of placental pathology and autopsy for more directed counseling. However, we note that this study also has limitations. Most significantly, consent for autopsy was not obtained in all cases of stillbirth. As more directive counseling was likely performed in cases where an autopsy was expected to yield the most information, these data may be biased in favor of autopsy. However as the majority (72.2%) of patients with stillbirth agreed to full autopsy, this bias is unlikely to explain the majority of observed benefit of an autopsy. In addition, these data are from an institution with a skill perinatal pathologist. Generalization to centers that do not utilize this expertise is more limited. This study predated the ACOG recommendation for microarray testing.[18] The increase in diagnosis associated with microarray may improve the yield of the clinical portion of the stillbirth evaluation.[19] Finally, while we attempted to ascribe alterations in clinical management afforded by the knowledge gained at each stage of evaluation, we recognize that there is some subjectivity in management decisions and our algorithms may not be applied to all cases.

In summary, these data indicate that a comprehensive stillbirth examination, including a detailed history, physical examination, laboratory assessment, placental pathologic exam, plus autopsy, reviewed in concert with an obstetrician yields significant information on both cause of death and recommendations for further clinical management. Autopsy may be less informative in specific cases (eg, clinically massive placental abruption, fetomaternal hemorrhage, antenatally diagnosed aneuploidy), but most clinically suspected categories of cause of death benefited from information generated by the autopsy. We believe these data can be used by obstetric caregivers to provide concrete information regarding the benefits of each step of expert pathologic examination in the setting of stillbirth and will serve to expand the physician-patient relationship by providing recommendations for anticipatory management of future pregnancies. ■

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