ARCHIVES of Pathology & Laboratory Medicine

Journal Information

Online ISSN: 1543-2165
Print ISSN: 0003-9985
Frequency: Monthly

Article Citation:
Lori M. Gawron, Cassing Hammond, and Linda M. Ernst (*2013*) Perinatal Pathologic Examination of Nonintact, Second-Trimester Fetal Demise Specimens: The Value of Standardization. Archives of Pathology & Laboratory Medicine: August 2013, Vol. 137, No. 8, pp. 1083-1087.

https://doi.org/10.5858/arpa.2012-0010-OA

ORIGINAL ARTICLES

Perinatal Pathologic Examination of Nonintact, Second-Trimester Fetal Demise Specimens: The Value of Standardization

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The authors have no relevant financial interest in the products or companies described in this article.

Presented in part as a poster at the Society for Pediatric Pathology Fall Meeting; October 2, 2011; Milwaukee, Wisconsin.

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Context.—Management of second-trimester intrauterine fetal demise via dilation and evacuation results in nonintact specimens for pathologic examination. Surgical pathology examination is often mandated; however, evidence on expected findings and specimen evaluation guidelines are lacking.

Objectives.—To assess pathologic findings of nonintact, second-trimester fetal demise specimens, through comparison of anatomic abnormalities identified on standardized perinatal examination to individualized general pathology examinations.

Design.—Single institution, retrospective chart review of 14- to 24-week gestational size fetal demise cases was conducted from May 2006 to October 2010. Suspected abnormalities, chromosomal and pathologic diagnoses were collected. A general surgical pathology examination occurred between May 2006 and October 2008, while a perinatal pathologist examined specimens between October 2008 and October 2010. Statistical analysis consisted of *t* tests and χ^2 tests by Stata/SE 12.1.

Results.—One hundred eighteen specimens were included and mean gestational size was 16.0 weeks (standard deviation, 1.6 weeks). Perinatal pathologic evaluation diagnosed significantly more abnormalities than did general pathologic examination (77.3% [34 of 44] versus 9.5% [7 of 75], $P < .001$). Forty-eight abnormalities were identified: 77.0% (n = 37) were placental and 23.0% (n = 11) were fetal. Chromosomal analysis was done on 73.7% (n = 87 of 118) with 12.6% (n = 11 of 87) showing abnormalities. Among aneuploid specimens, the perinatal pathologist confirmed abnormalities in 66.7% (n = 4 of 6) of cases while general pathologists confirmed abnormalities in 0% (n = 0 of 5) ($P = .02$).

Conclusions.—Systematic surgical pathology examination of nonintact, second-trimester fetal demise specimens yields increased information on fetal or placental abnormalities, which may be clinically useful. Institutions with high-risk obstetrical practices and dilation and evacuation providers should consider integrating a standardized perinatal checklist into educational and practice guidelines.

Accepted: October 17, 2012;

Intrauterine fetal demise (IUFD) in the second trimester (between 14- and 24-weeks' gestation) may be managed by induction of labor or surgically, via dilation and evacuation (D&E). Dilation and evacuation is the most common method of second-trimester uterine evacuation in the United States owing to its well-documented safety profile and numerous psychologic advantages to the bereaved patient.[1–3] Surgical management reduces maternal morbidity, compared to the labor induction process, if a physician trained in second-trimester D&E is readily available.[1,3] Patients have traditionally been counseled to undergo induction of labor if they desire higher-yield pathologic examination. This recommendation may be appropriate for women terminating a pregnancy for known fetal anomalies,[4] but evidence supporting the pathologic benefit of labor induction over D&E for women with a spontaneous fetal demise is lacking.

Pathologic examination of intact IUFD specimens, managed via labor induction, identifies abnormalities and informs the possible cause of death.[5] Since modern ultrasound technology identifies many morphologic abnormalities, researchers have questioned the added value of a pathologic examination.[6,7] However, most second-trimester patients have not yet undergone a full anatomic ultrasound evaluation at the time of fetal demise. In addition, in fetuses with known anomalies, studies[6,7] have reported pathologic identification of a number of abnormalities missed by ultrasonography.

When patients are diagnosed with a fetal demise, they want to know why it occurred and if it could happen in the next pregnancy. They may be presented with the option of an autopsy, but in most cases state law and/or institutional policies require surgical pathology examination applicable to all tissues obtained by surgical methods. No widely accepted, standardized anatomic examination guidelines currently exist for nonintact, second-trimester fetuses. The extent of examination varies with the pathologist and may range from reporting the presence or absence of fetal and placental tissue, as is typically done with first-trimester products of conception, to a more detailed, “mini-autopsy” examination. Currently, no data exist that would assist the obstetrician in counseling the patient on what information may be expected from a surgical pathology examination on a nonintact, fetal demise specimen. Since the examination is often mandated and paid for by the patient or her insurance, it stands to reason that the patient and the clinicians would like as thorough and detailed a pathologic examination as possible to address the cause of fetal death. The specialized training and expertise of pediatric and perinatal pathologists, when compared to a general pathologist, may alter the approach to examination in a way that is helpful to the clinicians and patients.

Therefore, our primary objective was to assess pathologic findings among nonintact, second-trimester fetal demise specimens at one institution, comparing the findings of a standardized examination by a perinatal pathologist to the findings by individual practice patterns of general surgical pathologists. Our secondary objectives were to describe anatomic abnormalities identified and assess the ability of pathologic examination to identify findings consistent with chromosomal derangements.

METHODS

We conducted a retrospective chart review approved by the institutional review board and received waiver of consent. The Enterprise Data Warehouse was queried for all patients aged 18 and older who were diagnosed with a second-trimester, spontaneous fetal demise and admitted to a single tertiary referral center between May 2006 and October 2010. Three general surgical pathologists examined all specimens obtained between May 2006 and October 2008. A single perinatal pathologist examined all specimens obtained between October 2008 and October 2010.

Exclusion criteria included (1) induced fetal demise for the purposes of pregnancy termination; (2) management via induction of labor; (3) fetal size less than 14-weeks' or greater than 24-weeks' gestation by ultrasonography; and (4) whether an autopsy was completed instead of a surgical pathology examination. The fetal size was used for the inclusion criteria for gestational age range instead of dating derived from ultrasonography or menstrual records for 2 reasons. First, most surgeons do not perform D&E procedures beyond 24-weeks' gestation; therefore, all larger specimens would be intact. Second, retention of the fetus may continue for several weeks. This difference in gestational age between dates and size gives an estimate of how long the fetus has likely been retained in the uterus, leading to maceration and examination difficulty.

The perinatal pathologist used a standardized examination checklist when evaluating specimens in surgical pathology (Figure). Briefly, for all of the D&E specimens examined by the perinatal pathologist, the tissues were initially sorted into 2 collections of tissue: the fetal tissues and the placental tissues. Fetal and placental tissues were each weighed separately and the weight recorded as a documentation of how much tissue was received. The fetal tissues were then oriented in anatomic position and photographed. The fetal parts were examined externally from head to toe, as is usually done for an intact fetal autopsy examination. If significant limb abnormalities were identified, radiographs of the bony tissues were obtained. Foot length was taken as a measure of fetal growth. In many cases, most of the thoracic and abdominal organs were not within their cavities and many were fragmented by the procedure. All of the tissue fragments received were examined for the presence of potential organ fragments and any anomalies recorded. The length, coiling pattern, the number of vessels, and the insertion site of the umbilical cord were all recorded. Any other cord abnormalities were also noted, such as knots, strictures, or masses. The membranes were inspected for color and insertion. The multiple fragments of villous parenchyma, some with overlying chorionic plate, were examined for lesions. Microscopic examination of fetal organs included assessment of appropriate maturation for gestational age, evidence of maceration changes, and identification of pathologic changes. The final surgical pathology report typically included diagnostic or at least descriptive statements about both the fetal and placental tissue.

A single reviewer (LG) extracted data from the computerized medical record. Estimated gestational age was based on earliest documented ultrasonography, and gestational size was based on the ultrasound findings documenting demise. Data collected included gestational age and size, suspected anomalies, pathologic findings by surgical pathologic examination, and chromosomal abnormalities. We also collected information about how chromosomes were collected and whether chromosomal derangements were confirmed by anatomic abnormalities on pathologic examination. The surgical pathology findings were organized into 2 categories: placental abnormalities and fetal abnormalities. Each specimen could have findings in both categories, for example, fetal hydrops along

with evidence of placental inflammation.

Statistical analysis was performed by using *t* tests for continuous variables and χ^2 test for categorical variables. The software package Stata/SE 12.1 (College Station, Texas) was used. As this is a descriptive study, no preliminary power analysis was completed. A post hoc power analysis using a test of equality of 2 proportions showed the sample size was sufficient with a power greater than .9 and $\alpha = .05$. The primary outcome sample size of 44 in the perinatal group with proportion of 77.3%, and sample size of 74 in the general group with proportion of 9.5%, were used in the analysis.

RESULTS

One hundred fifty-eight patients were identified by the chart query for IUFD; 32 were excluded owing to management via induction of labor and 8 were excluded owing to autopsy completion. One hundred and eighteen patients underwent D&E for fetal demise at 14- to 24-weeks' gestational size and had a surgical pathology examination during the study period of May 2006 to October 2010. The median maternal age was 34 years (range, 19–43 years) and median parity was 1.0 (range, 0–7). No significant differences were found between the gestational age and size of the specimens examined by the perinatal pathologist and those examined by the general surgical pathologists (overall mean size, 16.0 weeks [standard deviation, 1.6 weeks]) (Table 1).

The number of patients with ultrasound findings of fetal anomalies before demise and known to the pathologists before examination was low in both groups: 15.9% among perinatal pathologists (n = 7) versus 18.9% among general pathologists (n = 14) ($P = .68$). The ultrasound findings before demise consisted of cystic hygroma/hydropic changes (n = 11), monochorionic twins with growth restriction (n = 6), possible cardiac anomaly (n = 3), and oligohydramnios (n = 1). The perinatal pathologist correctly identified 57.1% of the ultrasound abnormalities (n = 4 of 7), including hydropic changes (n = 2), twin chronic abruption (n = 1), and tetralogy of Fallot (n = 1). The general pathologist correctly identified hydropic changes on 7.1% (n = 1 of 14) of those examined with known ultrasound findings.

The surgical pathology examination by a perinatal pathologist identified more abnormalities (77.3% [34 of 44]) than did the general pathologist group (9.5% [7 of 74]) ($P < .001$). A total of 48 abnormalities were identified in 40 specimens and are listed by examining pathologist in Table 2. Both groups most commonly identified placental abnormalities, but with greater frequency by the perinatal pathologist. Evidence of inflammation and maternal or fetal vascular anomalies were dominant, such as chronic intervillositis, hypercoiled cord with umbilical and chorionic thrombi, and chorionic hemosiderin deposition suggestive of previous intrauterine bleeding.

Fetal abnormalities accounted for 24.4% (n = 10 of 41) of those identified by the perinatal pathologist. These abnormalities included hydropic changes, structural anomalies, and growth restriction. Examples of structural findings include tetralogy of Fallot, malrotation of intestine, and horseshoe kidney. One fetal abnormality of hydropic changes suggestive of Turner syndrome was identified by the general pathologist group, although chromosomal culture results were inconclusive.

Most patients requested chromosomal analysis (n = 87 of 118), and no difference was observed in frequency of genetic abnormalities by examiner. There were a total of 11 aneuploid fetuses, including trisomies 13, 18, and 21, a triploid karyotype, Turner syndrome, and rare chromosomal aberrations. The perinatal pathologist identified anatomic findings on 66.7% (n = 4 of 6) of aneuploid specimens as compared to zero of those examined by the general pathologists ($P = .02$) (Table 1).

Chromosomal analysis was completed prenatally or at the time of ultrasonography, diagnosing demise for 14.9% (n = 13 of 87), and initiated for 85.1% (n = 74 of 87) at the time of the D&E procedure: 16.2% (n = 12 of 74) by amniocentesis in the operating room and the remainder by tissue culture from the placenta and fetal tissue. When chromosomal testing is pending at the time the pathologic specimen is received, anatomic findings may be classified as “suggestive of chromosomal abnormality” before the genetic results are obtained. Two cases had findings of “hydrops,” “massive hygroma,” and “villous edema” that were suggestive of aneuploidy, yet the chromosomal culture sent from placental tissue did not grow.

The perinatal pathologist documented anatomic abnormalities in 4 cases, which were confirmed to have abnormal chromosomes. For 1 case of Turner syndrome, “hydrops, dorsal edema of hands and feet, and intravillous calcifications” were noted. One fetus with trisomy 18 had a “2-vessel cord and small-for-gestational-age placenta.” A trisomy 21 fetus had “massive hydrops.” A fetus with “hydrops with an aortic arch abnormality” was found to have 47,*XY*,+mar on chromosomal analysis.

COMMENT

A total of 118 patients opted for surgical management of second-trimester fetal demise and declined autopsy, resulting in nonintact specimens for surgical pathology examination. The similar gestational age and size of the specimens in each group in this study rule out larger fetal size or greater maceration encountered by examiner as potentially affecting the level of examination difficulty. The perinatal pathologist identified significantly more fetal and placental abnormalities than the general pathologists. Abnormalities were also more likely to be identified by the perinatal pathologist in specimens that were subsequently found to have chromosomal derangements.

Most abnormalities identified by any examiner were placental. The general pathologists identified only 1 finding within the category of fetal abnormalities. These data suggest that examination of the fetal parts by general pathologists is frequently only a cursory examination to document fetal parts, potentially representing a general discomfort or unfamiliarity with characterization of fetal anomalies. Fetal demise in the second trimester should be seen as a diagnostic tool rather than a documentation examination. Many pathologists already use the diagnostic approach with missed abortion specimens in the first trimester. These data show that time invested in a nonintact, potentially macerated specimen still yields findings that may lead to a clinical diagnosis.

Literature is sparse on pathologic examination of IUFD specimens in the second trimester and it is lacking in nonintact demise specimens. Two studies demonstrate the utility of pathologic examination of an intact IUFD specimen after a labor induction. A Turkish study[5] of 2407 intact pregnancy terminations included 759 IUFD specimens between 10- and 24-weeks' gestation. Pathologists documented abnormal findings in 14.3% of specimens (n = 112 of 759) and findings other than congenital anomalies in 9.6% of specimens (n = 73 of 759), although the number identified through autopsy versus surgical examination was not included. A Swedish study[6] evaluating 188 intact IUFD specimens at greater than 22 weeks' gestation found that autopsy contributed to the diagnosis of cause of death in 36% of cases and placental pathologic examination contributed in 55% of cases, although only 18 specimens were at less than 24 weeks' gestation. The current study supports these findings in nonintact specimens, provided a standardized, perinatal pathologic examination is completed.

Several studies[7–10] have evaluated whether pathologic evaluation of intact fetal specimens confirms anomalous findings from prenatal ultrasonography. In second-trimester fetuses with known trisomy 21, pathologists found anomalies for 83.1% of 184 specimens, 60% of which were anticipated by ultrasonography.[9] In another study of 112 pregnancy termination specimens, ultrasound and final pathologic evaluation agreed in 45% of cases.[10] Pathologic examination yielded additional information among 40% of specimens. Central nervous system and cardiac anomalies had the greatest discordance between ultrasound and autopsy correlation, a finding consistent with a previous study on D&E specimens.[4] A case series of 37 nonintact fetuses terminated owing to congenital anomalies identified a major anomaly in 92% of cases.[11] In 46% of cases, a specific diagnosis was found only on pathologic examination. These findings show the value of using both ultrasonography and a careful pathologic examination as complementary means of evaluation, regardless of whether the specimen is intact.

Patients frequently request surgical management of second-trimester losses to avoid going through a labor and delivery experience.[2] This management choice does not change the patient request for answers as to why the fetal demise occurred. Many physicians offer autopsy rather than surgical pathology examination of the fetus, although evidence supporting the value of autopsy in nonintact specimens is limited and only in nondemise cases.[4,11] A pediatric or perinatal pathologist may not be available at all centers, and the lack of standardization for examination leaves a paucity of clinical counseling points about the possible findings of the examination.

When women return postoperatively, they request genetic and pathologic results, and documentation of “fetal parts and chorionic villi” does not contribute to the patient's or clinician's understanding of the loss. Noting anatomic abnormalities “suggestive of aneuploidy” gives a patient a plausible cause of death when the chromosomal culture does not grow. Evidence of chronic inflammation or a small-for-gestational-age placenta may be helpful to the patient when everything else appears normal. The surgical pathologic examination should be viewed as a valuable clinical tool, complementary to ultrasonography and chromosomal testing.

Pathologists and clinicians may use a classification system for stratification of autopsy findings to assist in counseling the bereaved family. One such system used in the literature for adult autopsy is based on a study that evaluated whether autopsy findings may have changed treatment or prolonged survival.[12] Parents experiencing an IUFD need a classification system similar to that described for pediatric deaths, which considers whether the information established a cause of death, whether it changes the patient's risk for a subsequent pregnancy, or affects the care of siblings.[13] In an Australian study of intact terminations for anomalies, the significant and major diagnostic determination allowed for alteration of risk counseling for subsequent pregnancies for 49.4% (n = 45 of 91) of those patients.[7] Until the examination of nonintact fetal demise specimens becomes standardized, the rate of identified abnormalities can only be estimated, limiting risk stratification for patient counseling.

The limitations of this study are inherent to a retrospective chart review. This is a descriptive study and a power calculation was not done, although post hoc power analysis showed sufficient sample size for primary outcome significance. Perinatal examinations were completed by only 1 pathologist and the perinatal pathologist did not review the general pathology specimens for missed abnormalities. The perinatal pathologist came to the institution in October 2008 and began evaluating most of these specimens; therefore, the standardized checklist has not been tested with the general pathologists in the same institution. The significant difference in findings between the perinatal and general pathologists may be due to increased time invested in a specimen or to subspecialty training in genetic anomalies specific to this population, although this will not be known until the examination is standardized for comparison. Whether the findings definitively diagnosed a “cause of death,” assisted with patient counseling, or changed risk stratification for the included patients are questions unanswered by the retrospective data.

Despite these limitations, this is the first descriptive study on this topic; it shows that a thorough and systematic approach to the pathologic examination of nonintact fetal demise specimens yields more information that may benefit the bereaved family. Future research should focus on implementation of a standardized examination checklist into general pathology practice in institutions with high D&E volume to assess if a standardized examination by a general pathologist yields the same results as that of a subspecialist. Dissemination of these findings may encourage more institutional investment into training of general pathologists or into adding a perinatal pathologist in centers with large high-risk obstetrical practices and trained D&E providers. These additions will improve collaboration between obstetricians and pathologists and allow patients to rely more on pathologic examinations to find a reason for fetal demise. Increased evidence supporting expected examination outcomes would justify the health care dollars spent on this often-mandated procedure.

CONCLUSION

Examination of second-trimester, nonintact fetal demise specimens should be viewed as a valuable diagnostic tool, not simply as a documentation examination. Implementation of a standardized, perinatal anatomic examination adds information with potential clinical implications, such as confirmation of suspected fetal abnormalities, identification of fetal and placental anomalies, and affirmation of anomalies consistent with chromosomal derangements. The use of an examination checklist developed by a perinatal pathologist may assist in educational settings and in standardization of practice patterns in institutions with large high-risk obstetrical practices and D&E providers. The increased reporting of pathologic findings may improve patient counseling and risk stratification and show value for the health care dollars spent on a commonly mandated examination.

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Standardized examination checklist.

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Table 1.
Pathologic Characteristics Stratified by Examining Pathologist

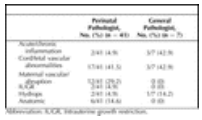

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Table 2.
Anatomic Abnormalities Identified on Surgical Pathology Examination

Cited by

Carolin A. Boecking, Eleanor A. Drey, Jennifer L. Kerns and Walter E. Finkbeiner. (2017) Correlation of Prenatal Diagnosis and Pathology Findings Following Dilation and Evacuation for Fetal Anomalies. *Archives of Pathology & Laboratory Medicine* **141**:2, 267-273.
Online publication date: 20-Oct-2016.
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M. Cristina Pacheco and Robyn C. Reed. (2017) Pathologist Effort in the Performance of Fetal, Perinatal, and Pediatric Autopsies: A Survey of Practice. *Archives of Pathology & Laboratory Medicine* **141**:2, 209-214.
Online publication date: 27-Oct-2016.
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