ARCHIVES of Pathology & Laboratory Medicine

Journal Information

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

Article Citation:
Linda M. Ernst, Lori Gawron, and Michael K. Fritsch (*2013*) Pathologic Examination of Fetal and Placental Tissue Obtained by Dilation and Evacuation. Archives of Pathology & Laboratory Medicine: March 2013, Vol. 137, No. 3, pp. 326-337.

https://doi.org/10.5858/arpa.2012-0090-RA

SPECIAL SECTION—CONTRIBUTIONS FROM THE ANATOMIC PATHOLOGY STAFF OF FEINBERG SCHOOL OF MEDICINE, NORTHWESTERN UNIVERSITY

Pathologic Examination of Fetal and Placental Tissue Obtained by Dilation and Evacuation

Linda M. Ernst, MD, MHS; Lori Gawron, MD; Michael K. Fritsch, MD, PhD

From the Departments of Pathology (Drs Ernst and Fritsch) and Obstetrics and Gynecology (Dr Gawron), Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Reprints: Linda Ernst, MD, MHS, Department of Pathology, Northwestern University Feinberg School of Medicine, Olson Pavilion, Room 2-461, 710 N Fairbanks Ct, Chicago, IL 60611 (e-mail: linda-ernst@northwestern.edu.)

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

Context.—Dilation and evacuation (D&E) is an alternative method to induction of labor for pregnancy termination and intrauterine fetal demise, and it is the most common mode of second-trimester uterine evacuation in the United States. Many D&E specimens are examined in surgical pathology, and there is little information available in surgical pathology textbooks or the literature to assist pathologists in these examinations.

Objective.—To provide an overview of the D&E procedure, discuss related legal issues, provide guidelines for routine pathologic examination of D&E specimens, and demonstrate the importance of careful pathologic examination of D&E specimens.

Data Sources.—Case-derived material and literature review.

Conclusions.—Pathologic examination of D&E specimens has been understudied. However, the available literature and our experience support the fact that careful pathologic examination of D&E specimens can identify significant fetal and placental changes that can confirm clinical diagnoses or provide definitive diagnosis, assist in explaining the cause of intrauterine fetal demise, and identify unexpected anomalies that may provide further clues to a diagnostic syndrome or mechanism of anomaly formation.

Accepted: May 1, 2012;

Table of Contents

Pathologic examination of products of conception in routine surgical pathology practice consists largely of the gross and microscopic examination of fragmented fetal and placental tissue from first-trimester missed or induced abortions. The majority of these pathology specimens are handled grossly by technicians, and for the most part, the main goal is the pathologic documentation of chorionic villi and fetal parts. However, pathologists, especially at large academic medical centers, are encountering an increasing number of disrupted, second-trimester fetal specimens for examination. Prior to the 1970s, uterine evacuation in the second trimester was accomplished via labor induction methods, such as prostaglandin or saline instillation, or by hysterotomy, and resulted in an intact fetus. The development of the dilation and evacuation (D&E) procedure during this time period gave an alternative to these methods. In 1974, only 36% of all midtrimester abortions were managed via D&E, but the safety and popularity of this method increased that number to 96% in 2005.[1]

The development of a fellowship in family planning in 1991 has trained a new generation of academic D&E providers. This is a 2-year postgraduate training program for obstetrician-gynecologists and focuses on advanced clinical skills, research, and teaching in the field of contraception and abortion. A total of 179 fellows have graduated, with 79% holding positions in academic centers.[2] The addition of a trained fellow to an institution will increase access to D&E services and allow women options for management of an unintended or abnormal pregnancy. Women have been shown to preferentially choose management via D&E over labor induction in the second trimester, avoiding an unpredictable labor experience.[3]

Given this shift in clinical obstetric practice, it is important for all surgical pathologists and technicians who examine D&E specimens to update their skills regarding the issues in second-trimester fetal and placental examination. Simple documentation of fetal parts and placental tissue is not adequate pathologic evaluation of these specimens. Important issues regarding quality assurance and future pregnancy counseling may need to be addressed, such as the cause of intrauterine fetal demise (IUFD), documentation/confirmation of anomalies seen on ultrasound, and recognition of fetal or placental abnormalities that may have genetic bases or recurrence risk. This review will provide a background review of the surgical and legal issues involved in D&E and provide a detailed review of the pathologic approach to these specimens, highlighting important aspects of the examination and providing guidelines for the examination.

DEFINITION OF D&E AND INDICATIONS FOR THE PROCEDURE

Dilation and curettage is performed in the first trimester, as the pregnancy is easily evacuated using mechanical cervical dilation and suction curettage. The traditional definition of dilation and curettage included sharp curettage, though this technique is now rarely used in the United States.[1] The resulting pathologic specimen is fragmented placental tissue and, depending on the gestational age and indications for the procedure, there may be small portions of the embryo/fetus identified. Extremities are usually the easiest embryonic/fetal tissues to identify, even though primary ossification centers are just beginning to develop. However, after 12 weeks' clinical gestational age, the fetal tissue becomes larger and the bony tissue is more calcified. Therefore, in the second trimester, D&E is performed because the procedure requires greater cervical dilation and advanced surgical skills for removal of the tissue.

Dilation and evacuation is performed as an outpatient surgical procedure. It typically begins with 1 to 2 days of cervical preparation to obtain adequate cervical dilation. This is accomplished with use of a series of laminaria tents, synthetic osmotic dilators, or a prostaglandin analogue, misoprostol.[4] The D&E procedure may be performed under any level of anesthesia, depending upon procedure location, patient tolerance, medical comorbidities, and gestational age. The fetal and placental tissue is then evacuated using a combination of suction and extraction forceps in multiple passes. This technique results in a fragmented fetus and placenta for pathologic examination.

Dilation and evacuation may be offered to women with cervical incompetence, IUFD, intrauterine growth restriction or placental insufficiency, fetal genetic or structural abnormalities, maternal health risk of continued pregnancy, or elective termination of pregnancy. Regardless of the indication for uterine evacuation, the D&E procedure remains the same.

The safety of the D&E procedure has been proven over time. The procedure itself has decreased morbidity for the patient compared with a misoprostol induction, if a provider is readily available.[5] In the early 1980s, a study[6] of 11 747 cases showed procedural complication rates to be low compared with older induction methods, with bleeding occurring in 1.4%, cervical laceration in 1%, fever in 0.8%, and uterine perforation in 0.4%. The complication rates were highest in the later gestational ages, likely because of increased passes with extraction forceps and more bony fragments for potential laceration. Two retrospective studies[7,8] have shown no significant increase in risks of preterm birth or adverse neonatal outcome in subsequent pregnancies in women who underwent a D&E.

LEGAL ISSUES IN HANDLING D&E SPECIMENS

The 2007 Supreme Court case *Gonzales v Carhart* upheld the federal Partial Birth Abortion Act of 2003 and altered the surgical options available to second-trimester D&E providers.[9] The Partial Birth Abortion Act of 2003 bans a procedure known as “intact D&E” or “dilation and extraction,” which involves greater cervical dilation, delivery of the fetus to the level of the cranium, and decompression of the cranium to allow passage through the cervix. The procedure decreases the number of instrument passes for a potentially safer extraction, minimizes the risks of retained tissue, and allows for a more intact specimen for pathologic examination.[10] In a 2004 study,[11] 120 intact procedures were compared with 263 standard D&E procedures. Complication rates were similar between the D&E group (4.9%, n = 13 of 263) and the intact group (5.0%, n = 6 of 120), with genital laceration and bleeding being the most common. The authors, at that time, recommended leaving the procedural decision up to the physician based upon intraoperative findings.[11]

This ban has potentially affected the pathologic examination in 2 ways. First, providers are required to perform a standard D&E in all cases, leading to increased fragmentation of fetuses for pathologic examination. Second, many providers are performing a feticidal injection of digoxin or potassium chloride prior to cervical preparation. This allows for compliance with the ban, as the law applies only when a “living fetus” is present at the outset of evacuation.[9] The effects of the injection on the quality of the pathologic examination, especially cardiac structures, are not usually considered. In our experience, intracardiac KCl injection predominantly alters the gross and microscopic features of the cardiac structures. The ventricular septum is frequently disrupted or so soft it disintegrates upon opening the heart, making examination for ventricular septal defects difficult. The lateral ventricular walls are also very soft and easily disrupted with manipulation. The great vessel anatomy is typically preserved. Microscopically, the myocardium shows advanced autolytic-like changes with loss of cellular detail.

The US Supreme Court has held that a woman's right to an abortion is not absolute and that states may restrict or ban abortions after fetal viability. Therefore, state interpretations and restrictions may vary. Many states limit abortion procedures after viability, as in our state of Illinois. Although viability is commonly interpreted as 24 weeks, and in no cases less than 20 weeks, a determination of viability is to be made on an individual basis. The Illinois Abortion Act specifically defines viability as "that stage of fetal development when, in the medical judgment of the attending physician based on the particular facts of the case before him, there is a reasonable likelihood of sustained survival of the fetus outside the womb, with or without artificial support."[12] Some states have limits on abortion based on specific gestational age requirements. Six states ban abortion at 20 weeks' gestation.[13] These legal issues may affect the gestational age up to which a surgical termination of pregnancy can be performed, and subsequently determine the kinds of specimens received by the pathology department.

Historically, pathology departments have required consent for examination of intact fetuses 20 weeks or greater and consider these to be autopsy specimens; however, because the tissues acquired by D&E are the result of a surgical procedure and do not produce an intact fetus, they are generally examined in surgical pathology. *Human tissues* removed in the operating room of most hospitals are subject to pathologic examination by law or institutional policy with a few exceptions (ie, toenails, hardware, tonsils in some pediatric hospitals). Therefore, D&E specimens are surgical pathology specimens in most instances. At our institution, all D&E specimens receive a pathology examination and most are routine surgical pathology examinations. For surgical pathology examination no additional patient consent is required; however, the patients are informed that the examination is routine and consent for the examination is covered by general hospital consent for treatment. In some cases, particularly when the history includes IUFD or complex fetal anomalies, especially of the skeletal system, or when the patient/family desires an autopsy, an autopsy on the products of a D&E can be requested and will be performed at any gestational age. Autopsy examination is performed only if a valid, signed autopsy consent is received.

THE TYPICAL APPEARANCE OF THE D&E SPECIMEN

The appearance of the D&E specimen at the pathology gross bench can vary widely. This variation in appearance of the fetal and placental tissues depends on a multitude of variables such as gestational age at time of the procedure, level of cervical dilation, anomalies present in the fetus, and skill of the operator. In our experience, it is very rare for a completely intact fetus to be the product of a D&E procedure; however, it has been seen in cases where cervical dilation and fetal size allow for the near delivery of the fetus at the beginning of the D&E procedure, essentially not requiring any suction or extraction.

In the majority of the cases there is some level of fetal fragmentation. Collapse of the skull bones and fragmentation of the soft brain tissue is the most frequent finding in D&E specimens, precluding, in most cases, assessment of fetal brain anomalies. More frequently, the fetal body may be partially intact, and incision of the thoracic and/or abdominal wall may be required to examine the internal viscera. However, the most frequent finding is significant fragmentation of the fetal tissues, with many of the thoracic and abdominal viscera as loose tissues not positioned in their respective body cavities.

Placental fragmentation is also frequent in D&E specimens. However, in most cases there is a portion of recognizable chorionic plate that can be assessed. Umbilical cord is also frequently identified and can be assessed for number of umbilical vessels and coiling pattern in most cases. The cord is frequently fragmented, so length of the cord depends on aggregate measurement and the assumption that all the cord is received. Insertion of the umbilical cord can only sometimes be assessed. Membranes are usually identified in most cases and can be sampled for histology. Maternal surface/basal plate is probably the least likely to be intact among the placental tissue fragments. If parenchymal lesions such as infarcts or intervillous thrombi are present, these can be identified grossly among the fragments of placental tissue.

STANDARD OF CARE FOR PATHOLOGIC EXAMINATION OF D&E SPECIMENS

There are good references available for consultation regarding performance of intact fetal autopsy,[14–16] and techniques/guidelines for the gross examination of most surgical pathology specimens are available in manuals.[17–19] However, although many of these manuals contain information about fetal examination, specific information about how to handle fragmented fetuses is provided only in rare instances.[19] Additionally, there is a paucity of literature that deals directly with pathologic evaluation of specimens from D&E procedures. The first description in the literature of the pathologic examination of D&E specimens described a systematic approach, similar to the method used at our institution and detailed below in this review.[20]

The lack of relevant literature regarding the examination of D&E specimens may reflect an acceptance of the overlap of the examination with the intact fetal examination. However, fragmented fetuses are mostly dissected in surgical pathology and finalized by pathologists who do not normally perform fetal autopsy. A study[21] at our institution has shown that in the hands of general surgical pathologists the examination of D&E specimens lacks important findings that are seen by more experienced, trained perinatal pathologists. Because not all institutions can employ a fetal/perinatal pathologist, there is a need for general pathologists to begin to acquire skills necessary to adequately examine tissues from D&E specimens.

Trained pathologists' assistants can be an important part of the team to handle D&E surgical pathology specimens. With appropriate training in fetal examination and a standardized approach to the examination, most of the D&E specimens can be initially assessed by the pathologists' assistant, photographed, and described. Consultation with the attending pathologist can occur after the initial triage of the specimen by the pathologists' assistant, and if necessary the attending pathologist can review the gross specimen with the pathologists' assistant to confirm anomalies and provide teaching points when relevant. Histologic sampling is then guided by what tissues are identified and what anomalies are seen.

Initially there may be some individuals who express discomfort with grossing D&E specimens; however, most of these apprehensive feelings can be overcome with a standardized approach to the examination that can keep the individual focused on the anatomic and pathologic issues. It is also helpful for these individuals to attend combined clinical/pathology conferences where findings from the D&E cases are presented in order to understand the relevance and value of the pathologic examination in the larger clinical context.

PROCEDURES FOR PATHOLOGIC EXAMINATION OF D&E SPECIMENS

The overall purposes of the pathologic examination of D&E specimens are listed in Table 1. The approach to D&E specimens at our institution is a systematic examination of the fetal and placental tissues. The immediate goals of the pathologic examination are (1) documentation of fetal parts, assessment of growth and maturation, and characterization of any fetal anomalies and (2) characterization

of any placental abnormalities.

Surgical Pathology Examination

For all the D&E specimens examined in surgical pathology, the tissues are initially sorted into 2 collections of tissue, the fetal tissues and the placental tissues. Fetal and placental tissues are each weighed separately and the weight recorded. The fetal tissues are then oriented in anatomic position and photographed. The fetal parts are examined externally from head to toe, as is usually done for an intact fetal autopsy examination. Although the skull is typically collapsed and head circumference is not usually measured, the skull bones are examined for defects to indicate the presence of encephalocele. The scalp skin can be identified in most cases and assessed for level of fetal maturation by examining the presence of scalp hair. Scalp defects (aplasia cutis) should also be sought. The completeness of the face varies from case to case, but an effort should be made to examine eyes, nose, lips and mouth, palate, and ears. The neck is frequently disrupted, making the confirmation of prenatally diagnosed cystic hygroma difficult. The thorax is usually disrupted, but fragments of ribs can usually be identified. Their number cannot usually be accurately assessed. Some, but usually not all, thoracic organs may remain within the thorax. The abdominal wall is usually disrupted, so assessment of anterior abdominal wall defects can be limited. However, the insertion site of the umbilical cord into the abdominal wall should be sought. Some abdominal, retroperitoneal, or pelvic organs may remain in their cavities. In most cases, 4 extremities can be identified, and the absence of an extremity should be documented. The limbs are examined for bony anomalies and the fingers/toes, nails, and creases are examined on all intact feet and hands. Foot length is recorded as a critical anatomic parameter to estimate gestational age, using standard reference ranges.[22] Fragments of cervical, thoracic, and lumbar spine are almost always identified and the posterior aspect should be examined. Frequently neural tube defects can be identified with accuracy, although seldom is the spinal cord available for examination. Table 2 outlines the external anomalies to seek in the pathologic examination of D&E specimens.

In many cases, most of the thoracic and abdominal organs are not within their cavities, and many are fragmented by the procedure. All the tissue fragments received should be examined for the presence of potential organ fragments. Table 3 shows the percentage of time various fetal organs are identified in second-trimester D&E examination at our institution. The heart is identified in most cases, but can show variable disruption. If it is found mostly intact, the heart still frequently remains partially disrupted at the base. Detailed cardiac examination is performed whenever the heart is preserved, and in our experience approximately 44% of the time a detailed examination is possible when the heart is identified. Lung tissue is also found frequently in D&E specimens, although fragmentation often limits the assessment of lobation. Among abdominal/retroperitoneal organs, loops of bowel and/or stomach are identified in nearly all cases. One or both kidneys are usually found; however, the ureters and bladder are seldom available for adequate assessment. The liver, adrenal glands, spleen, and pancreas are identified with decreasing frequency. The external and/or internal reproductive organs are identified up to 62% of the time, making assessment of gender possible in those cases. The diaphragm is usually disrupted. Tables 4 and 5 provide an overview of our experience with D&E specimens and identification of major anomalies.

If there are obvious anomalies noted on the examination of individual organs, these are isolated and photographed. All organs or potential organs grossly identified are submitted for routine histologic examination in 2 or 3 cassettes. Examples of typically sampled tissues include kidney, adrenal gland, liver, lung, heart, gonads, and bowel fragments. Radiographs are taken if skeletal dysplasia is suspected, but are not routinely performed at our institution as part of a surgical pathology examination. Similarly, microbiology studies are not a routine part of examination of these surgical specimens. Cytogenetic studies are frequently indicated for D&E specimens. At our institution, the specimen for karyotype is usually taken in the operating room by the surgeon performing the D&E, and the specimen is sent directly to the laboratory. A study[23] has shown a 98.8% success rate when fetal and placental tissues are harvested immediately after the D&E procedure. For IUFD, studies[24–28] have shown that tissue taken by amniocentesis has a better yield than tissues submitted from the fetus after delivery. However, if cytogenetic analysis is desired and was not obtained in the operating room or by amniocentesis, it can be acquired in pathology. A sample of fetal tissue and/or placental tissue should be collected in a sterile fashion and stored in nutrient media for its rapid transport to the cytogenetics laboratory. One study[29] of postmortem cytogenetic analyses showed that the site of the sample did not influence the success rate of the culture, but a longer interval between delivery and sampling did negatively impact the success rate.

The placental fragments are also examined grossly. The largest recognizable placental fragment usually includes the chorionic plate surface, and the size of this fragment is recorded. The length, coiling pattern, and number of vessels noted in the umbilical cord are recorded. If the insertion site of the cord can be determined, that is also recorded. Any other abnormalities of the cord, such as knots, strictures, or masses, are also noted. Membrane color and insertion, if identified, is recorded. The multiple fragments of villous parenchyma are examined for lesions. All placental fragments, excluding umbilical cord, are weighed, recorded, and compared with standard charts of expected values.[30] Routine histologic sections include umbilical cord, membranes if identified, and 2 or 3 portions of placental villi (full thickness if possible) to include chorionic and basal plates. Figure 1 shows the template that is used for recording data regarding the gross examination of D&E specimens at our institution.

The final surgical pathology report should include diagnostic or at least descriptive statements about both the fetal and placental tissue. Microscopic examination of fetal organs includes assessment of appropriate maturation for gestational age, evidence of maceration changes, and identification of pathologic changes. Discussion of all microscopic pathologic changes potentially seen in fetuses of D&E specimens is beyond this scope of this review, but categories of pathology that can be identified included microscopic changes associated with infection, malformation syndromes, intrauterine fetal death, and fetal stress. Similarly, most of the placental changes can be classified as maternal vascular pathology, fetal vascular pathology, infectious pathology, and chronic inflammatory pathology. We use a standard format for reporting our surgical pathology findings in D&E specimens (see Figure 2). This report includes the use of foot length and placental weight as measures of growth/gestational age.[22,30] Typically, a microscopic description is included as part of the report, and finally a note is added to indicate that fragmentation of the fetal and placental tissues limits/precludes gross assessment and characterization of all fetal anomalies.

Autopsy Examination

Pathologic examination of the D&E specimen can proceed as an autopsy if a properly completed and signed autopsy consent form is received. The approach to D&E specimens for which an autopsy examination is requested is similar to the surgical pathology examination. Examination proceeds as outlined above for surgical specimens with the following modifications: radiographs are routinely performed for all cases; full body and detailed organ photographs are taken for all cases; all or most internal organs are examined, weighed, and sampled for histologic examination; cytogenetics are routinely performed if not previously performed as part of the clinical workup; and microbiology remains optional, dependent on the clinical history. Additional laboratory testing can also be requested if deemed necessary by the staff pathologist. Additional histology sections are submitted in all autopsy cases, including all potential

organs. A provisional autopsy report is issued within 2 working days of the initial prosection reporting gross findings. A detailed final autopsy report including final anatomic diagnoses, a summary of the clinical history, a detailed description of gross and microscopic examinations, and finally a clinicopathologic correlation is issued within 60 working days of the gross examination.

Recently the American Board of Pathology[31] adopted a new policy regarding inclusion of fetal autopsies among the 50 autopsies required for trainees in pathology in order to sit for the Anatomic Pathology Board examination in 2013. In the description of the new policy, the board states that only autopsies on intact fetuses can be included in the 50 required autopsies, even when a valid autopsy permit is received and all the procedures outlined above are performed. No such limitations are placed on adult autopsy, and limited/partial adult autopsies are performed commonly and counted toward board certification without question. This decision by the American Board of Pathology may reflect a lack of understanding of several issues regarding D&E specimens, such as variability in gestational age, variability in fragmentation, and the important information that can be gained from both a clinical and educational perspective from examination of fragmented fetuses. Furthermore, the American Board of Pathology policy underscores the need for more research in this field to educate pathologists and clinicians, raise the standards for examination of these specimens, and legitimize all fetal and placental examinations, even when performed on fragmented specimens.

Disposition of Fetal Remains

Products of conception, including D&E specimens, are unique among the surgical pathology specimens because the family can request a private cremation or burial for the specimen, which is considered the fetal remains. When such a request is made by the family, the tissues remaining after surgical pathology or autopsy examination are released to a licensed funeral director for final disposition. This may require the examination of the fetal tissues in a fairly expedited manner by the pathologist, and release of the tissues prior to the typical 2 weeks after signout afforded most surgical pathology specimens.

VALUE OF CAREFUL EXAMINATION OF D&E SPECIMENS

There are several studies[18,32–47] that have reviewed the correlation between prenatal ultrasound and autopsy findings, all based on examination of intact fetuses. Agreement between prenatal ultrasound findings and autopsy diagnosis when autopsy is performed on an intact fetus ranges from 45% to 91.2%. These data are typically used to indicate the quality of the prenatal diagnoses, with the autopsy findings representing the gold standard. In addition, several studies[33,35,42,43,46] indicate that the intact fetal autopsy reveals additional important findings not diagnosed prenatally, thus establishing the importance of fetal autopsy both for quality assurance and for diagnosis of disease, with potential implications for family planning, recurrence risk, and genetic counseling.

However, there is a paucity of literature examining the value of examination of the fragmented fetal and placental tissues obtained from D&E procedures. To our knowledge, the first description of a cohort of patients undergoing D&E and pathologic examination appeared in 1990.[48] The authors reported on 60 consecutive patients who underwent D&E for second-trimester pregnancy termination, and stated that prenatal diagnoses were confirmed in all cases. However, the pathologic analysis of the specimens was not well described. The first description of the detailed pathologic examination of D&E specimens was published in 1995.[20] The author carefully examined the pathologic specimens from 37 D&E procedures performed for fetal indications and showed that major pathologic findings are seen in up to 92% of the cases examined. The author noted that some major clinical diagnoses can be difficult to confirm on D&E, including Dandy-Walker malformation, Arnold-Chiari malformation, encephalocele, holoprosencephaly, cystic hygroma, endocardial cushion defect, severe fetal hydrops, and diaphragmatic hernia. However, in 46% of the cases a specific diagnosis was obtained only by the pathologic examination. Another study[44] performed to assess the correlation between prenatal ultrasound diagnoses and pathologic findings was published in 1999. In addition to investigation of intact fetal specimens, this study included analysis of 36 fragmented fetuses. For the examination of fragmented fetuses, the authors concluded that neural tube defects could be confirmed 90% of the time, but central nervous system and visceral anomalies were confirmed in only a minority of cases. A pediatric pathologist reviewed reports for this study, and when necessary the gross specimens and histology slides, but the details of the pathologic examination were not reported.

In our experience, the pathologic examination of tissues obtained from D&E for fetal indications can provide important information in the following categories: (1) confirming the clinical diagnosis based on ultrasound findings; (2) giving a definitive diagnosis when the clinical diagnosis includes a differential diagnostic list; and (3) diagnosing unexpected anomalies that may be isolated or provide further clues to a diagnostic syndrome or mechanism of anomaly formation. To illustrate these 3 categories of diagnostic importance, case examples follow:

Case 1

A 36-year-old gravida 5, para 2-0-2-2 woman at 14 5/7 weeks' gestation underwent D&E for fetal anomalies. The prenatal ultrasound showed multiple congenital anomalies including encephalocele, bilateral enlarged kidneys, abnormal lower distal limbs, club foot, and polydactyly. There was a clinical suspicion of Meckel-Gruber syndrome. Figure 3, A through G, shows the gross and microscopic findings from the examination of the D&E specimen. Examination of the fragmented fetus helped to further confirm the diagnosis of Meckel-Gruber syndrome by confirming the polydactyly and defining the kidney pathology as bilateral multicystic dysplasia. In addition, the finding of ductal plate malformation in the liver was further support for Meckel-Gruber syndrome.[49,50]

Case 2

A 33-year-old gravida 2, para 0 woman at 22 5/7 weeks' gestation underwent D&E for fetal anomalies. Prenatal ultrasound showed a large cardiac mass with both cystic and solid components, associated with a pericardial effusion. The differential diagnosis included rhabdomyoma, teratoma, fibroma, and a possible lung lesion impinging upon the heart. The heart was identified among the loose fetal organ fragments; however, a cardiac mass was not seen. A separate ovoid mass measuring 3.2 × 2.1 × 1.0 cm and weighing 5.2 g was seen. It did not appear to be a specific organ fragment. The mass showed both solid and cystic components on gross examination and histology was consistent with immature teratoma. Microscopically, at one edge of the tumor, it was closely associated with pericardium, implying that the likely origin for the cardiac mass was the pericardium[51,52] (see Figure 4, A through D).

Case 3

A 40-year-old woman at 16 weeks' gestation underwent D&E for fetal acrania diagnosed on ultrasound. Examination of the fragmented fetal tissues showed evidence of a cranial defect. In addition, examination of the extremities showed strands of membranous tissue wrapped around the fingers and attached to the lower extremity, consistent with amnion bands (see Figure 5, A through D). These

findings suggested that the mechanism of the cranial defect was more likely a disruption sequence than a primary malformation. Defining the mechanism of the anomaly can change genetic counseling. Amnion rupture sequence is generally a nonrecurrent condition, whereas acrania/anencephaly has a 1% to 2% recurrence risk, and generally high-dose folate supplementation is also recommended.[53,54]

Case 4

A 34-year-old woman at 20 weeks' gestation underwent D&E for fetal hydrocephalus. The fetus was classified as male by identification of both the internal and external genitalia at pathologic examination. The head and brain were too disrupted to make a definitive diagnosis of hydrocephalus, but the hands appeared abnormal with adducted thumbs (see Figure 6, A through C). The finding of adducted thumbs associated with hydrocephalus is suggestive of X-linked hydrocephalus and related syndromes.[55–57] Based on these pathologic findings from the D&E specimen, targeted genetic testing of the *L1CAM* gene was performed, and the fetus showed a deletion of the *L1CAM* gene. The mother was subsequently identified as a carrier. The family is opting for preimplantation genetic testing in subsequent pregnancies.

In addition to fetal indications for pregnancy termination such as fetal genetic abnormalities, structural anomalies, or growth restriction, D&E is a surgical option when IUFD is diagnosed. Pathologic evaluation of D&E specimens for midtrimester IUFD has not been studied in the literature to our knowledge. However, there are several recent studies[58–63] that have examined the value of pathologic examination of the fetus and placenta for intact fetuses in setting of IUFD, and the American College of Obstetricians and Gynecologists[64] recommends autopsy and placental evaluation be offered for all stillbirths. A study of the Stillbirth Collaborative Research Network[58] involving 663 stillbirths in both the second and third trimesters, and including postmortem examinations in more than 500 patients, showed that 66% of stillbirths have at least 1 positive result among the 3 major components of the evaluation: perinatal autopsy, placental examination, or karyotype. Similarly, a Swedish study[62] evaluating 188 intact IUFD specimens at less than 22 weeks' gestation found that autopsy and placental examination were the most valuable diagnostic examinations, helping them to identify a causative factor associated with death in 91% of cases. So, it is logical to infer that evaluation of IUFD in D&E specimens, if performed rigorously, should also be useful in evaluating cause of fetal death. Our group[21] has recently performed an institutional retrospective chart review to assess the findings of pathologic examination of disrupted second-trimester fetal demise specimens. 118 specimens were evaluated between May 2006 and October 2010, and the findings of a perinatal pathologist were compared with those examined by general pathologists. Specialized perinatal pathologic evaluation diagnosed significantly more abnormalities than general pathologic examination. Abnormalities identified included infection, maternal or fetal vascular abnormalities, findings suggestive of aneuploidy, fetal growth restriction, hydrops, and other anatomic anomalies. Similar to the conclusions from many of the autopsy studies, we concluded that implementation of a standardized, anatomic examination on disrupted D&E specimens from second-trimester fetal loss frequently confirms clinically suspected anomalies and identifies unanticipated fetal or gestational abnormalities, and that these findings yield clinically useful information for patient counseling.[21] Further studies are needed to determine if the examination of D&E specimens for IUFD is more limited than an autopsy and placental examination on an intact fetus.

CONCLUSIONS

Pathologic examination of D&E specimens has been understudied. However, the available literature and our experience support the fact that careful pathologic examination of D&E specimens can identify significant fetal and placental changes that can confirm clinical diagnoses, provide definitive diagnosis from clinical differential diagnostic lists, assist in explaining the cause of IUFD, and identify unexpected anomalies that may provide further clues to a diagnostic syndrome or mechanism of anomaly formation. Therefore, careful examination of D&E specimens can influence clinical care by potentially influencing family planning, genetic counseling, and grief management.

For their untiring assistance with D&E specimens at Northwestern Memorial Hospital, we thank Papreddy Kashireddy, MD, PA (ASCP) CM, and Anthony Sellner, MHS, PA (ASCP) CM. For her assistance with discussion of legal issues, we thank Jennifer W. Benton, RN, JD.

References

1. Gamble SB, Strauss LT, Parker WY, Cook DA, Zane SB, Hamdan S. Abortion surveillance—United States, 2005. *MMWR Surveill Summ*. 2008;57(13):1–32. [Google Scholar]

2. Landy U, Darney PD. The future of contraception: the future leaders of family planning. *Am J Obstet Gynecol*. 2011;205(4)(suppl):S29–S33. [Crossref] [Medline] [Google Scholar]

3. Grimes DA, Smith MS, Witham AD. Mifepristone and misoprostol versus dilation and evacuation for midtrimester abortion: a pilot randomised controlled trial. *BJOG*. 2004;111(2):148–153. [Crossref] [Medline] [Google Scholar]

4. Newmann SJ, Dalve-Endres A, Diedrich JT, Steinauer JE, Meckstroth K, Drey EA. Cervical preparation for second trimester dilation and evacuation. *Cochrane Database Syst Rev*. 2010;(8):CD007310. [Medline] [Google Scholar]

5. Edlow AG, Hou MY, Maurer R, Benson C, Delli-Bovi L, Goldberg AB. Uterine evacuation for second-trimester fetal death and maternal morbidity. *Obstet Gynecol*. 2011;117(2, pt 1):307–316. [Crossref] [Medline] [Google Scholar]

6. Peterson WF, Berry FN, Grace MR, Gulbranson CL. Second-trimester abortion by dilatation and evacuation: an analysis of 11,747 cases. *Obstet Gynecol*. 1983;62(2):185–190. [Medline] [Google Scholar]

7. Jackson JE, Grobman WA, Haney E, Casele H. Mid-trimester dilation and evacuation with laminaria does not increase the risk for severe subsequent pregnancy complications. *Int J Gynaecol Obstet*. 2007;96(1):12–15. [Crossref] [Medline] [Google Scholar]

8. Kalish RB, Chasen ST, Rosenzweig LB, Rashbaum WK, Chervenak FA. Impact of midtrimester dilation and evacuation on subsequent pregnancy outcome. *Am J Obstet Gynecol*. 2002;187(4):882–885. [Crossref] [Medline] [Google Scholar]

9. Partial-Birth Abortion Ban Act of 2003, 18 USC §1531 (2003). [Google Scholar]

10. Hammond C. Recent advances in second-trimester abortion: an evidence-based review. *Am J Obstet Gynecol*.

2009;200(4):347–356. [Crossref] [Medline] [Google Scholar]

11. Chasen ST, Kalish RB, Gupta M, Kaufman JE, Rashbaum WK, Chervenak FA. Dilation and evacuation at >or=20 weeks: comparison of operative techniques. *Am J Obstet Gynecol*. 2004;190(5):1180–1183. [Medline] [Google Scholar]

12. Illinois Abortion Law of 1975. ILCS ch 720, §510. [Google Scholar]

13. Guttmacher Institute. State policies on later abortions. State Policies in Brief. http://www.guttmacher.org/statecenter/spibs/spib_PLTA.pdf. Published 2011. Accessed December 2, 2011. [Google Scholar]

14. Valdes-Dapena M, Huff DS. *Perinatal Autopsy Manual*. Washington, DC: Armed Forces Institute of Pathology/American Registry of Pathology; 1983. [Google Scholar]

15. Gilbert-Barness E, Debich-Spicer DE. Handbook of Pediatric Autopsy Pathology. Totowa, NJ: Humana Press Inc; 2005. [Google Scholar]

16. Siebert JR. Perinatal, fetal, and embryonic autopsy. In: Gilbert-Barness E, ed. *Potter's Pathology of the Fetus, Infant, and Child*. 2nd ed. Philadelphia, PA: Mosby Elsevier; 2007:695–739. [Google Scholar]

17. Rosai J, Ackerman LV. *Rosai and Ackerman's Surgical Pathology*. 9th ed. Edinburgh, Scotland: Mosby; 2004. [Google Scholar]

18. Weston MJ, Porter HJ, Andrews HS, Berry PJ. Correlation of antenatal ultrasonography and pathological examinations in 153 malformed fetuses. *J Clin Ultrasound*. 1993;21(6):387–392. [Crossref] [Medline] [Google Scholar]

19. Lester SC. *Manual of Surgical Pathology*. 3rd ed. Philadelphia, PA: Saunders/Elsevier; 2010. [Google Scholar]

20. Klatt EC. Pathologic examination of fetal specimens from dilation and evacuation procedures. *Am J Clin Pathol*. 1995;103(4):415–418. [Crossref] [Medline] [Google Scholar]

21. Gawron LM, Hammond C, Ernst LM. Perinatal pathologic examination of non-intact, second trimester fetal demise specimens: the value of standardization. In press. [Google Scholar]

22. Hansen K, Sung CJ, Huang C, Pinar H, Singer DB, Oyer CE. Reference values for second trimester fetal and neonatal organ weights and measurements. *Pediatr Dev Pathol*. 2003;6(2):160–167. [Crossref] [Medline] [Google Scholar]

23. Bernick BA, Ufberg DD, Nemiroff R, Donnenfeld A, Tolosa JE. Success rate of cytogenetic analysis at the time of second-trimester dilation and evacuation. *Am J Obstet Gynecol*. 1998;179(4):957–961. [Crossref] [Medline] [Google Scholar]

24. Brady K, Duff P, Harlass FE, Reid S. Role of amniotic fluid cytogenetic analysis in the evaluation of recent fetal death. *Am J Perinatol*. 1991;8(1):68–70. [Crossref] [Medline] [Google Scholar]

25. Bryant Borders AE, Greenberg J, Plaga S, et al. Value of amniocentesis versus fetal tissue for cytogenetic analysis in cases of fetal demise. *Fetal Diagn Ther*. 2009;26(2):81–84. [Crossref] [Medline] [Google Scholar]

26. Neiger R, Croom CS. Cytogenetic study of amniotic fluid in the evaluation of fetal death. *J Perinatol*. 1990;10(1):32–34. [Medline] [Google Scholar]

27. Saal HM, Rodis J, Weinbaum PJ, DiMaggio R, Landrey TM. Cytogenetic evaluation of fetal death: the role of amniocentesis. *Obstet Gynecol*. 1987;70(4):601–603. [Medline] [Google Scholar]

28. Smith A, Bannatyne P, Russell P, Ellwood D, den Dulk G. Cytogenetic studies in perinatal death. *Aust N Z J Obstet Gynaecol*. 1990;30(3):206–210. [Crossref] [Medline] [Google Scholar]

29. Kyle PM, Sepulveda W, Blunt S, Davies G, Cox PM, Fisk NM. High failure rate of postmortem karyotyping after termination for fetal abnormality. *Obstet Gynecol*. 1996;88(5):859–862. [Crossref] [Medline] [Google Scholar]

30. Benirschke K, Kaufmann P, Baergen RN. *Pathology of the Human Placenta*. 5th ed. New York, NY: Springer; 2006. [Google Scholar]

31. American Board of Pathology. Policy for fetal autopsies. http://www.abpath.org/FetalAutopsyPolicy.pdf. Accessed December 15, 2011. [Google Scholar]

32. Amini H, Antonsson P, Papadogiannakis N, et al. Comparison of ultrasound and autopsy findings in pregnancies terminated due to fetal anomalies. *Acta Obstet Gynecol Scand*. 2006;85(10):1208–1216. [Crossref] [Medline] [Google Scholar]

33. Antonsson P, Sundberg A, Kublickas M, et al. Correlation between ultrasound and autopsy findings after 2nd trimester terminations of pregnancy. *J Perinat Med*. 2008;36(1):59–69. [Medline] [Google Scholar]

34. Chescheir NC, Reitnauer PJ. A comparative study of prenatal diagnosis and perinatal autopsy. *J Ultrasound Med*. 1994;13(6):451–456. [Crossref] [Medline] [Google Scholar]

35. Clayton-Smith J, Farndon PA, McKeown C, Donnai D. Examination of fetuses after induced abortion for fetal abnormality. *BMJ*. 1990;300(6720):295–297. [Crossref] [Medline] [Google Scholar]

36. Isaksen CV, Eik-Nes SH, Blaas HG, Tegnander E, Torp SH. Comparison of prenatal ultrasound and postmortem findings in fetuses and infants with congenital heart defects. *Ultrasound Obstet Gynecol*. 1999;13(2):117–126. [Crossref] [Medline] [Google Scholar]

37. Isaksen CV, Eik-Nes SH, Blaas HG, Torp SH. Comparison of prenatal ultrasound and postmortem findings in fetuses and infants with central nervous system anomalies. *Ultrasound Obstet Gynecol*. 1998;11(4):246–253. [Crossref] [Medline] [Google Scholar]

38. Johns N, Al-Salti W, Cox P, Kilby MD. A comparative study of prenatal ultrasound findings and post-mortem examination in a tertiary referral centre. *Prenat Diagn*. 2004;24(5):339–346. [Crossref] [Medline] [Google Scholar]

39. Kaasen A, Tuveng J, Heiberg A, Scott H, Haugen G. Correlation between prenatal ultrasound and autopsy findings: a study of second-trimester abortions. *Ultrasound Obstet Gynecol*. 2006;28(7):925–933. [Crossref] [Medline] [Google Scholar]

40. Manchester DK, Pretorius DH, Avery C, et al. Accuracy of ultrasound diagnoses in pregnancies complicated by suspected fetal anomalies. *Prenat Diagn*. 1988;8(2):109–117. [Crossref] [Medline] [Google Scholar]

41. Medeira A, Norman A, Haslam J, Clayton-Smith J, Donnai D. Examination of fetuses after induced abortion for fetal abnormality—a follow-up study. *Prenat Diagn*. 1994;14(5):381–385. [Crossref] [Medline] [Google Scholar]

42. Phadke SR, Gupta A. Comparison of prenatal ultrasound findings and autopsy findings in fetuses terminated after prenatal diagnosis of malformations: an experience of a clinical genetics center. *J Clin Ultrasound*. 2010;38(5):244–249. [Medline] [Google Scholar]

43. Shen-Schwarz S, Neish C, Hill LM. Antenatal ultrasound for fetal anomalies: importance of perinatal autopsy. *Pediatr Pathol*. 1989;9(1):1–9. [Crossref] [Medline] [Google Scholar]

44. Sun CC, Grumbach K, DeCosta DT, Meyers CM, Dungan JS. Correlation of prenatal ultrasound diagnosis and pathologic findings in fetal anomalies. *Pediatr Dev Pathol*. 1999;2(2):131–142. [Crossref] [Medline] [Google Scholar]

45. Szigeti Z, Csaba A, Pete B, Hajdu J, Papp Z, Papp C. Correlation of prenatal sonographic diagnosis and morphologic findings of fetal autopsy in fetuses with trisomy 21. *J Ultrasound Med*. 2007;26(1):61–68; quiz 69–70. [Crossref] [Medline] [Google Scholar]

46. Tennstedt C, Chaoui R, Bollmann R, Korner H, Dietel M. Correlation of prenatal ultrasound diagnosis and morphological findings of fetal autopsy. *Pathol Res Pract*. 1998;194(10):721–724. [Medline] [Google Scholar]

47. Rutledge JC, Weinberg AG, Friedman JM, Harrod MJ, Santos-Ramos R. Anatomic correlates of ultrasonographic prenatal diagnosis. *Prenat Diagn*. 1986;6(1):51–61. [Crossref] [Medline] [Google Scholar]

48. Shulman LP, Ling FW, Meyers CM, Shanklin DR, Simpson JL, Elias S. Dilation and evacuation for second-trimester genetic pregnancy termination. *Obstet Gynecol*. 1990;75(6):1037–1040. [Medline] [Google Scholar]

49. Blankenberg TA, Ruebner BH, Ellis WG, Bernstein J, Dimmick JE. Pathology of renal and hepatic anomalies in Meckel syndrome. *Am J Med Genet Suppl*. 1987;3:395–410. [Crossref] [Medline] [Google Scholar]

50. Loo CK, Freeman B, Killingsworth M, Wu XJ. An immunohistochemical study of human fetal liver in the Meckel-Gruber syndrome. *Pathology*. 2005;37(2):137–143. [Crossref] [Medline] [Google Scholar]

51. Tollens M, Grab D, Lang D, Hess J, Oberhoffer R. Pericardial teratoma: prenatal diagnosis and course. *Fetal Diagn Ther*. 2003;18(6):432–436. [Crossref] [Medline] [Google Scholar]

52. Fagiana AM, Barnett S, Reddy VS, Milhoan KA. Management of a fetal intrapericardial teratoma: a case report and review of the literature. *Congenit Heart Dis*. 2010;5(1):51–55. [Crossref] [Medline] [Google Scholar]

53. Jones KL, Robinson LK, Benirschke K. Evaluation of the cranial base in amnion rupture sequence involving the anterior neural tube: implications regarding recurrence risk. *Birth Defects Res A Clin Mol Teratol*. 2006;76(9):688–691. [Crossref] [Medline] [Google Scholar]

54. Padmanabhan R. Etiology, pathogenesis and prevention of neural tube defects. *Congenit Anom (Kyoto)*. 2006;46(2):55–67. [Crossref] [Medline] [Google Scholar]

55. Finckh U, Schroder J, Ressler B, Veske A, Gal A. Spectrum and detection rate of L1CAM mutations in isolated and familial cases with clinically suspected L1-disease. *Am J Med Genet*. 2000;92(1):40–46. [Crossref] [Medline] [Google Scholar]

56. Jouet M, Rosenthal A, Armstrong G, et al. X-linked spastic paraplegia (SPG1), MASA syndrome and X-linked hydrocephalus result from mutations in the L1 gene. *Nat Genet*. 1994;7(3):402–407. [Crossref] [Medline] [Google Scholar]

57. Vos YJ, de Walle HE, Bos KK, et al. Genotype-phenotype correlations in L1 syndrome: a guide for genetic counselling and mutation analysis. *J Med Genet*. 2010;47(3):169–175. [Crossref] [Medline] [Google Scholar]

58. Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. *JAMA*. 2011;306(22):2459–2468. [Medline] [Google Scholar]

59. Bonetti LR, Ferrari P, Trani N, et al. The role of fetal autopsy and placental examination in the causes of fetal death: a retrospective study of 132 cases of stillbirths. *Arch Gynecol Obstet*. 2011;283(2):231–241. [Crossref] [Medline] [Google Scholar]

60. Ceylaner G, Ceylaner S, Gunyeli I, Ekici E, Celasun B, Danisman N. Evaluation of 2407 fetuses in a Turkish population. *Prenat Diagn*. 2007;27(9):800–807. [Crossref] [Medline] [Google Scholar]

61. Kidron D, Bernheim J, Aviram R. Placental findings contributing to fetal death, a study of 120 stillbirths between 23 and 40 weeks gestation. *Placenta*. 2009;30(8):700–704. [Crossref] [Medline] [Google Scholar]

62. Petersson K, Bremme K, Bottinga R, et al. Diagnostic evaluation of intrauterine fetal deaths in Stockholm 1998–99. *Acta Obstet Gynecol Scand*. 2002;81(4):284–292. [Medline] [Google Scholar]

63. Tellefsen CH, Vogt C. How important is placental examination in cases of perinatal deaths? *Pediatr Dev Pathol*. 2011;14(2):99–104. [Medline] [Google Scholar]

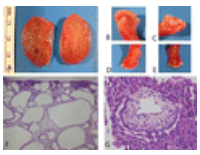
64. ACOG Practice Bulletin No. 102: management of stillbirth. *Obstet Gynecol*. 2009;113(3):748–761. [Medline] [Google Scholar]

View larger version (22K)

Figure 1.
Sample dilation and evacuation template used for gross examination.

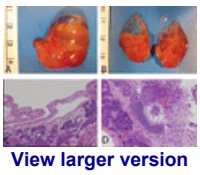
View larger version (23K)

Figure 2.
Sample surgical pathology template for diagnosis of second-trimester dilation and evacuation specimens.



View larger version (126K)

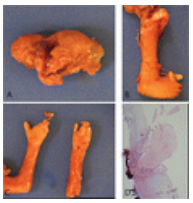
Figure 3.
Dilation and evacuation case 1. A, Gross photograph of kidney tissue found among loose organs. Note diffuse cystic change. B, Gross photograph showing hexadactyly of the left hand. C, Gross photograph showing hexadactyly of the right hand. D, Gross photograph showing hexadactyly of the left foot. E, Gross photograph showing hexadactyly of the right foot. F, Photomicrograph of kidney showing multicystic dysplasia characterized by ovoid cysts of varying sizes and intermittent loss of nephrogenic zone. G, Photomicrograph of liver showing ductal plate malformation characterized by a ring of bile duct epithelium at the edge of the portal tract (hematoxylin-eosin, original magnifications ×20 [F] and ×40 [G]).



View larger version (136K)

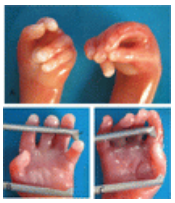
Figure 4.
Dilation and evacuation case 2. A, Gross photograph of mass found among loose organs. It was not attached to the heart, which was found separately. B, Gross photograph of the cut surface of the mass showing both cystic and solid components. C, Photomicrograph of the mass showing glandular elements in close association with mesothelial-lined pericardium. D, Photomicrograph of mass showing glandular and cartilaginous elements (hematoxylin-eosin, original magnifications ×20).

Figure 5.
Dilation and evacuation case 3. A, Gross photograph of skull defect. B, Gross photograph of the foot displaying a membranous band extending from the lower leg to the toe. C, Gross photograph of the



View larger version (172K)

hands demonstrating bands of membranous tissue wrapped around the fingers. D, Photomicrograph of the band attached to the lower leg composed of predominantly fibrous tissue (hematoxylin-eosin, original magnification ×4).



View larger version (131K)

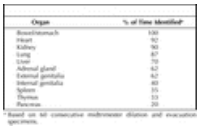
Figure 6.
Dilation and evacuation case 4. A, Gross photograph of bilateral hands. Note the overlapping fingers and adducted thumbs. B and C, Gross photographs of the hands demonstrating adducted thumbs.

View larger version (17K)

Table 1.
Purposes of Dilation and Evacuation Examination

View larger version (13K)

Table 2.
External Anomalies to Seek in Gross Examination of a Fragmented Fetus



View larger version (14K)

Table 3.
Fetal Tissues Identified in Dilation and Evacuation Specimens

View larger version (27K)

Table 4.
Confirmation of Clinical Diagnosis by Pathologic Examination of Dilation and Evacuation (D&E) Specimen

View larger version
(8K)

Table 5.
Findings on Dilation and Evacuation (D&E) Examination Suspicious for Specific Genetic Abnormality

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.
Abstract | Full Text | PDF (111 KB) | Supplemental Material | Track Citations(RSS | Email)

Glenn P. Taylor, Ona Marie Faye-Petersen, Linda Ernst, Robin D. LeGallo, Galen M. Schauer, Alex K. Williamson and M. Cristina Pacheco. (2014) Small Patients, Complex Challenging Cases: A Reappraisal of the Professional Efforts in Perinatal Autopsies. *Archives of Pathology & Laboratory Medicine* **138**:7, 865-868.
Online publication date: 3-Feb-2014.
Citation | Full Text | PDF (68 KB) | Track Citations(RSS | Email)

top