Stillbirth Investigations: An Iconographic and Concise Diagnostic Workup in Perinatal Pathology

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Abstract

Introduction Stillbirth is a dramatic event for the parents, health care team, and anyone close to the expectant parents. Multidisciplinary team (MDT) meetings are essential to improve communication in health care. We review the most frequent findings discussed at MDT meetings.

Methods A PubMed search was conducted through December 2021 since the inception (1965) using clinical queries with the key terms "stillbirth" AND "investigation" AND "pathology" AND "human." The search strategy included reviews, meta-analyses, randomized controlled trials, clinical trials, and observational studies. This systematic review is based on, but not limited to, the search results. It is the experience of more than 30 years of pediatrics, obstetrics, and pathology staff.

Results Two hundred and six articles were screened and complemented through the perusal of congressional activities and personal communications. Pathological findings following perinatal death can be divided into macroscopic, histologic, and placental findings. The placenta is crucial in fetal medicine and is key in determining the cause of stillbirth in a substantial number of events. Perinatal lung disease is essential to evaluate the response of newborns to extrauterine life and address newborns' outcomes appropriately.

Conclusions Stillbirth remains one of the less explored areas of medicine, and we can determine the cause in a limited number of cases. Nevertheless, placental pathology is critical in the etiology discovery pathway. Accurate investigations and discussion of photography-supported findings are vital in promoting communication at MDT meetings.

Keywords
- Perinatal Investigation
- stillbirth
- intrapartum distress
- early neonatal illness

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Introduction

Stillbirth is a dramatic event for the parents, health care team, and anyone close to the expectant parents. In case of death, after parental consent is obtained, a postmortem examination can elucidate a series of fetal medicine events that may help for the cause and mechanism of death.[1,2] A granted postmortem investigation is a straightforward examination, which can be promptly performed once clinical notes are available to the pathologist. Communication failure between clinicians and pathologists represents a significant issue in patient safety, risk management, and performance improvement in health care.[3] Pathologists are critical in health care because of their precious interaction with clinicians and parents.[4] Either the failure to identify the cause of death or the absence of feedback may jeopardize proper health care delivery. However, the autopsy also harbors some limitations. They include the potential restriction of the examination to only some organ cavities, the intrinsic snapshot on the time-reduced examination, the absence of placenta accompanying the fetus or newborn, the number of hours of intrauterine exposure to the maceration of the fetal tissues, and the expertise of the pathologist or pathology team. These are probably the most important drawbacks to the autopsy procedure, but some authors can precept others. A routine autopsy has no specific recommendations from the World Health Organization (WHO). Still, several perinatal societies favor the perinatal autopsy not only to identify the cause of death but also to help the family in the mourning process, and laboratory information systems may help in collecting proper health data to public health agencies.[4,5] The three reasons for neonatal/perinatal mortality in developing countries are prematurity, sepsis/pneumonia, and asphyxia. In this manuscript, we are not going to identify differences between low- and high-income countries, although it will be one of the next topics of our public health research group. Multidisciplinary team (MDT) meetings are crucial in health care.[6] The lack of adequate MDT meetings may have the potential consequence of perpetuating the decline of the worldwide autopsy rate. We aim to review the most frequent perinatal diseases discussed at MDT meetings.

Methodology

A PubMed search was conducted through December 2021 since the inception using clinical queries with the key terms "stillbirth" AND "investigation" AND "pathology" AND "human." The search strategy included reviews, meta-analyses, randomized controlled trials, clinical trials, and observational studies. This systematic review is based on, but not limited to, the search results. It is the experience of more than 30 years of pediatrics, obstetrics, and pathology staff. There are several pediatric pathology textbooks, but this iconographic and concise review focuses on perinatal results that may be useful in a residency teaching setting and improve communication at the MDT meetings.

Results

Two hundred and six articles were screened and complemented through the perusal of congressional activities and personal communications. Pathological findings following perinatal death can be divided into macroscopic, histologic, and placental findings. The placenta is crucial in fetal medicine and is key in determining the cause of stillbirth in a substantial number of events. Perinatal lung disease is essential to evaluate the response of newborns to extrauterine life and address newborns' outcomes appropriately. The results are organized in subsections of macroscopy, histology, and placenta.

Macroscopy

This section includes both external and internal macroscopic features. However, most of them are general findings, and none of them are specific enough to help a physician to write up a death certificate. External components to include are size variations (i.e., small for dates with evidence of uteroplacental insufficiency, fetal growth restriction [FGR], and macrosomia), molding stains and effects, evidence of presenting part, forceps marks, meconium remnants on infant (i.e., vernix, external auditory meatus, nails, etc.), petechial- and asphyxia-related (large) hemorrhages (i.e., pleural, epicardial, and thymic petechiae, periductal [ductus arteriosus/ductus Botalli] bleedings, adrenal hemorrhage, subcapsular hemorrhage, and pulmonary hemorrhage), and evidence of swallowing of meconium or moderate amount of amniotic fluid rests in the retropharynx, larynx, trachea, and bronchi. Traces of meconium may be recognizable in skin creases or ears, even if the infant has been thoroughly cleaned before presentation to the parents. Petechiae are essential to identify and count and are present in areas of the skin subjected to increased capillary pressure (e.g., legs and lower trunk in breech delivery, head in case of cord strangulation during cephalic delivery, a single limb that has prolapsed through the cervix). Red-brown discoloration of the buttocks can indicate an underlying sacrococcygeal teratoma. This is a handy clue during the inspection of the fetus or newborn (►**Figs. 1** and **2a,b**).

Examining the head is also relevant for identifying an abnormal occipital shape due to osteodiastasis. Occipital osteodiastasis occurs at all gestational ages, from 27 weeks up to the term. If minor displacement is present, it may be insignificant, but if displacement is significant, it would suggest birth trauma. Major displacement points to distortion and obstruction of venous sinuses in the posterior fossa or direct pressure on the cerebellum and brainstem. It has a rapidly fatal outcome. Tense fontanels may indicate brain swelling, such as if the infant was maintained on a ventilator for several days. A significant cause of death is posterior fossa hemorrhage following birth trauma. Sources of bleeding into this site include the superior cerebellar veins, which drain into the Galen and straight sinus vein, and the occipital sinuses.

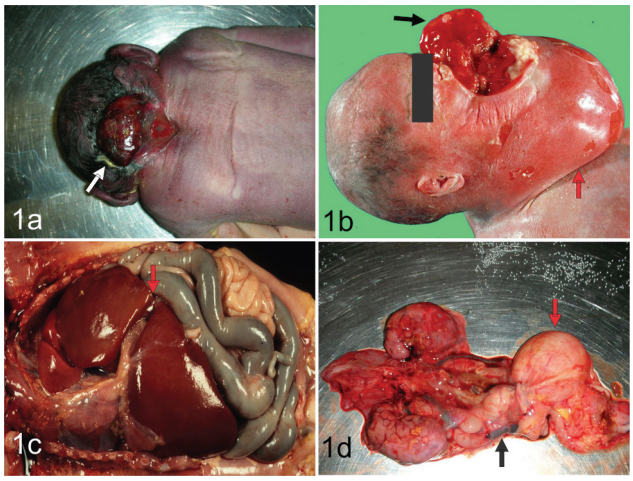

Fig. 1 (**a**) A neural tube defect of superior type showing an encephalocele (*arrow*) in a preterm baby. (**b**) Epignathus in a late gestation fetus. Epignathus is a form of oropharyngeal teratoma. It arises from the palate and is due to unorganized and uncontrolled differentiation of somatic cells. Although the epignathus is considered benign from the histopathological point of view, it is life-threatening because of its atypical features (size, location, and rate of development) and high risk of airway obstruction occurs. Epignathus is the cause of death in 80 to 100% of the cases recognized at the time of delivery. Gross photograph as a kind contribution of Dr. N. Sarioglu of the Campus Charite, Berlin, Germany. (**c**) Congenital diaphragmatic defects can be incompatible with life. Here is the autopsy view of the thoracic and abdominal cavities of a preterm infant with Wolf–Hirschhorn disease. There is a large defect of the left diaphragm with upward displacement of the abdominal viscera and extreme hypoplasia of both lungs. The female infant weighed 830 g (1,375 ± 281 g) and had a head circumference of 24 cm corresponding to a 26-week gestation fetus. The infant showed bradycardia and no spontaneous breathing. The abdomen was sunken and chest X-ray revealed a diaphragmatic defect, bilateral lung hypoplasia, and a shift of the mediastinum to the right. A chromosomal imbalance with 46, XX, del (4) (pter-p13) was diagnosed, while the parental chromosomes were numerically and structurally normal. (**d**) A preterm infant showing hydroureteronephrosis with megacystis due to urethral posterior valve and dysplasia of the cystourethral connection.

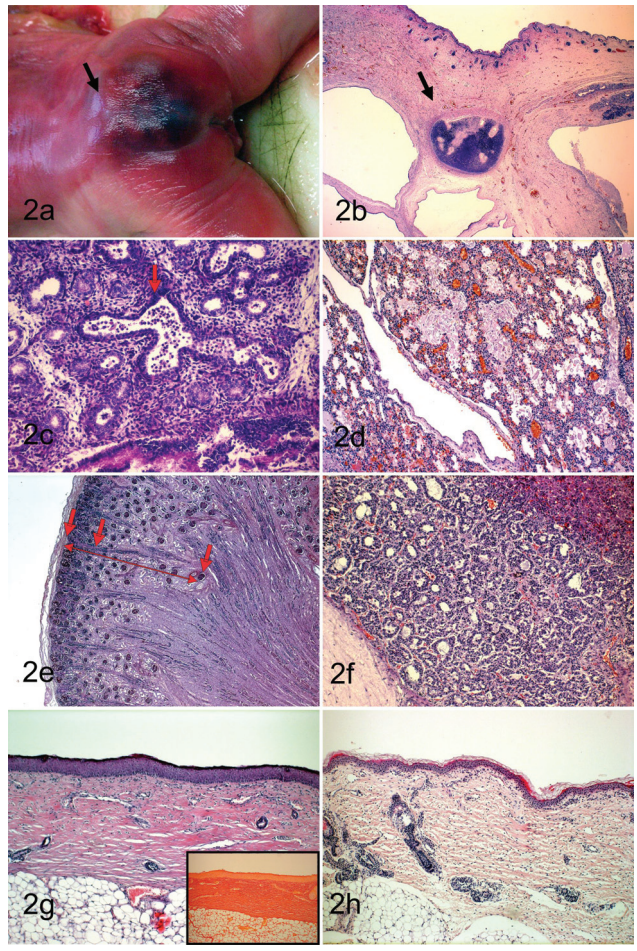

Fig. 2 (**a**) The perineal region of this 22 weeks' gestation baby shows a red-brown swelling (*arrow*) on the bottom. (**b**) Histologic examination of the perineal tissue shows a teratoma with cysts of different size and three-layer differentiation (ectodermal, endodermal, and mesodermal). The coccyx is shown in the center of the picture (hematoxylin and eosin staining, 20×). (**c**) Neutrophilic granulocytes in the lumina of a lung at the canalicular stage of differentiation (hematoxylin and eosin staining, 200×). A major lumen is shown (*arrow*). (**d**) Focal inspissation of epithelial squames in the alveolar lumina (*arrow*) of a lung from a baby who died of respiratory failure (hematoxylin and eosin staining, 100×). (**e**) The thickness of the glomerulogenic zone (zone delimitated by the first *two arrows* from left to right) and its ratio to the definitive zone (zone delimitated by the *first arrow* and the *last arrow* from left to right) are very helpful to assess renal maturity (hematoxylin and eosin staining, 40 ×). (**f**) Cystic pseudofollicular change (*arrow*) of the definitive due to focal degeneration of the adrenal cortical cells (hematoxylin and eosin staining, 100×). (**g**) The skin of a baby with restrictive dermopathy, a genodermatosis, shows thickened, hyperkeratotic epidermis, a dermis composed of dense parallel connective tissue, and a thick layer of adipose and fibrous connective tissue in the hypodermis (hematoxylin and eosin staining, 100×). In the inset, there is a tissue section from the same specimen showing no elastic fibers (Elastica van Gieson staining, 100×). (**h**) Normal skin of a baby age-matched to 1 g (hematoxylin and eosin staining, 100×.

The main internal features of acute asphyxia are congestion with organ hemorrhage, including lungs and parietal pleura, heart, thymus, liver, and adrenal glands. On examination of the heart, petechiae are often distributed along the line of the coronary arteries. In the lung parenchyma, massive pulmonary hemorrhage can occur in birth asphyxia. It develops almost immediately after birth and has its zenith several hours after birth. It can be due to consumption coagulopathy owing to disseminated intravascular coagulation. Brain changes vary with the asphyxia pattern and the time of the infant's death. There is a range of findings, from generalized congestion without apparent brain swelling to pallor, swelling, flattening of the brain surface, and obliteration of sulci to frank intraventricular and parenchymal hemorrhage.

Difficulties in detecting pathologic changes may be compounded by a delay between fetal death and delivery. To identify the intrauterine growth correctly, it is necessary to correlate the pattern of growth and maturation of the fetus to the time of fetal death rather than the time of delivery, which may often be complicated. There may be limited information on the time the fetus died, the fetal tissues may have lost weight following fetal death, and the maceration process may obscure structural details on which the growth pattern assessment might be based. The personal information of the

mother is critical, precisely at which time fetal movements ceased and when the fetal heart could no longer be heard.[7] Cessation of recognition of fetal movements is usually followed by fetal death within 24 hours. The use of modern electronic recording helps avoid the mistake of identifying maternal tachycardia as a fetal cardiac impulse, fetal bradycardia as a maternal pulse, or the co-twin in twin pregnancy. The detaching of the epidermis from the dermis on applying oblique pressure (skin slippage) is the first sign of maceration, which first appears around 6 hours after death. It consistently presents if the infant has been dead in utero for 12 hours or more.[8–10] Bullae formation due to fluid collection beneath the epidermis appears 24 hours after death. If these *bullae* are ruptured during labor, the infant will show a raw-weeping body surface. Progressive hemolysis results in a uniform red-purple discoloration of the internal organs. The exudation of hemolyzed blood into the connective tissue delivers a progressive softening (maceration) of all internal organs. After 5 to 7 days, the dura separates from the cranial bones. By this stage, examining the brain in toto with the dura is helpful. The rate and nature of the maceration process vary with the infant's gestational age, the underlying pathologic conditions, microbiology, and the temperature of the infant's body until a postmortem examination is performed. An immature growth-restricted infant may change its tissue color to yellow-brown due to its relatively low soft-tissue mass and blood volume (*fetus papyraceous*).[11] It is important to stress that the maceration process may alter body weight and length. In fact, the longer the fetus has been dead in utero, the less reliable such information will be.

Particular attention should be given to nuchal hygroma and hydrops fetalis, which are separate but commonly coexistent conditions exhibiting a spectrum of severity. A nuchal hygroma is an accumulation of lymphatic and interstitial fluid in the posterior tissues of the fetal and neonatal neck due to a failed or delayed connection of the embryonic jugular lymphatic sac with the developing left subclavian/jugular veins. Fetal hydrops or hydrops fetalis represents a more diffuse accumulation of excess fetal water with edema in at least two body sites (e.g., skin, thorax, and abdomen). There are three main etiological groups for fetal hydrops, including (1) cardiovascular or pneumological issues, (2) severe anemia (e.g., thalassemia or infections), and (3) genetic or developmental syndromes, including monosomy X0 (Turner's syndrome), multiple pterygium syndrome, Brachmann de Lange syndrome, tuberous sclerosis complex (Bourneville–Pringle disease), myotonic dystrophy, and Neu–Laxova syndrome.[12–17] In addition, an underlying metabolic disorder may overlap the three groups and needs to be carefully screened.[16]

Regarding nonimmune hydrops fetalis (NIHF), Kurdi interrogates the medical community if fetal medicine experts are doing the appropriate test each time.[18] NIHF is diagnosed when there is evidence of fluid accumulation in at least two extravascular spaces. A long list of causes has been found to be strongly associated with NIHF. If thorough investigations are performed, which also include a complete postmortem examination, an underlying cause can be pinpointed in up to 84% of such fetuses. Nevertheless, intrauterine fetal death can jeopardize the etiologic clarification. The success rate for identifying an etiology for the NIHF drops to 40% if an intrauterine fetal death occurs.[19] Dramatically, the identification of hydrops by ultrasound may start a very frustrating journey for the family and physicians because it eventually requires extensive searches for the etiology with the involvement of tertiary and quaternary health care centers.

A nuchal hygroma or fetal cystic hygroma is detected in 1/120 early ultrasonograms and 1/6,000 births and is defined as an increase of the nuchal fold thickness (sonolucent) of more than 6 mm. Antenatal detection of nuchal hygroma is associated with poor prognosis,[20] but not all fetuses with nuchal hygroma develop hydrops. One should keep in mind the possible reversibility of this lesion. If the lymphatic connection is at least partially active by midgestation, the distended lymphatic cisterns and channels may collapse, and their fluid may return to the intravascular space. This aspect is crucial for the clinician and the pathologist, who can receive an infant without apparent evidence of nuchal hygroma. A nuchal hygroma is due to chromosomal abnormalities in ~85% of cases, with monosomy X being the most common chromosomal anomaly,[21] followed by trisomy 21. In patients without evidence of a nuchal hygroma, some external features may suggest chromosomal abnormalities such as nuchal skin redundancy, abnormal posterior hairline, low-set and posteriorly positioned ears, anteverted ears, and widely spaced nipples. Nuchal hygroma has been associated with chromosomal abnormalities in up to 80% of cases.[10] The most common karyotype abnormalities include trisomy 21, trisomy 18, trisomy 13, and monosomy X (Turner's syndrome). A nuchal hygroma is accompanied by a poor prognosis, and there is a rate of 1/750 among fetal losses due to this condition. Nuchal hygroma can be associated with a genetic syndrome and harbor a normal karyotype. The syndromes include Noonan's syndrome, Apert's syndrome, Fryns' syndrome, Pena–Shokeir syndrome, Cornelia de Lange syndrome, achondroplasia, lethal multiple pterygium syndrome, congenital heart disease, and fetal alcohol syndrome.[22–27]

Hydrops fetalis is defined by detecting two or more abnormal fluid collections (ascites, pleural effusion, pericardial effusion, or shin edema) in the fetus by sonography.[28] It affects 1 in 1,700 to 3,000 pregnancies and is associated with worrisome perinatal sequelae, including preterm birth, mirror syndrome, intrauterine fetal death, or neonatal death. If appropriate Rh(D) immune globulin administration is performed, only 10% of hydrops fetalis can be associated with alloimmunization, and 90% involve a range of several etiologies, including infections, karyotype abnormalities, inborn errors of metabolism, and fetal structural anomalies in the setting of multiple congenital anomaly syndrome.[28] Recognizing non-immune-mediated hydrops fetaalis or fetal hydrops (NIHF) is essential for the relationship to intrauterine fetal death, which is essentially a hypoxia-/asphyxia-related death. Fetuses affected with immune-mediated fetal hydrops are euvolemic to hypovolemic. It is due to accumulations of fluid in body cavities, and tissues are usually

hypoproteinemic. The placenta is not a passive transport sponge, receiving ~40% of fetal cardiac output. In hypoxia, fetal cardiac output is redistributed to favor the fetal head, upper extremities, and placenta. Reducing oncotic pressure and increased hydrostatic pressure in the fetal villous capillaries results in excessive fluid in the maternal space. Thus, hemolysis leads to hypoxic organ and endothelial cell damage, leading to a loss of endothelial tight junctional integrity and capillary leakage. In addition, fluid and plasma proteins leak into the interstitium, serosal cavities, and placental villous stroma, compounding hypovolemia with compensatory tachycardia, complicating increased venous pressure and decrease of lymphatic flow in the fetus without lymphatic return from the placenta. The impairment of the placental villous transport of oxygen, amino acids, and other essential anabolites with the further compromise of plasma protein and blood volume and ongoing hemolysis, hypoxia, and damage will lead to death.[29,30] Thus, fetal death in immune-mediated fetal hydrops is due to hypoxia and stillborn. Newborns who survive following intrauterine umbilical vessel transfusions may show ischemic damage and infarctions in the heart and other viscera. They include the liver, brain, and gut, with increased extramedullary hematopoiesis in the liver, spleen, thymus, lymph nodes, endocrine organs, body wall, and interstitium. Other key features include hyaline membrane disease, intraventricular hemorrhage, and dysmaturity of chorionic villi. The prognosis of fetuses with NIHF is severe. These fetuses seem to behave better than their immune-mediated counterparts, and this aspect has been associated with the underlying etiology.[31–34] The value of perinatal autopsy in nonimmunological fetal hydrops is remarkable, and a postmortem investigation will provide helpful information in the majority of cases.[35,36]

Trauma is a severe and body-altering physical injury, and significant cranial or intracranial trauma is found in 9.1% of intrapartum and first-week deaths.[37] Trauma contributes to death in about one-fourth of cases and is evenly distributed among birth weights in proportion to mortality rates. Regarding the trauma to the head, many of the traumatic lesions are not in themselves lethal but are markers of excessive compression of the head and brain. Compression of the brain produces a similar pattern to birth asphyxia. Many infants labeled as asphyxiated may indeed be victims of cerebral compression. Most fatal injuries to the head and neck are not easily recognizable clinically and are hurriedly labeled as asphyxia before postmortem examination. Clearly, some of these lesions are extremely important to be detected and differentiated, and a careful review of this anatomic region should be performed at all times. These lesions include caput succedaneum, subaponeurotic hemorrhage, cephalohematoma, extradural hemorrhage, and skull fracture. The occipital osteodiastasis (i.e., disruption of syndesmosis between squamous and lateral parts of occipital bone) is due to excessive pressure on the suboccipital region. A breech delivery (i.e., delivery of the head in occipitoposterior position or rotational forceps for transverse arrest) causes distortion or disruption of venous sinuses in the posterior fossa or compression or laceration of the brainstem and cerebellum. Subdural hemorrhage is due to tearing of venous sinuses in tentorial tears or tearing of bridging veins more often. Tentorial tears are usually due to oblique compressions, such as forceps. When dural tears occur without bleeding, they are probably significant and must be comprehensively discussed at the MDT meetings. They may represent a marker of compression sufficient to have caused brain damage. Dissection of the spinal cord to rule out injuries is extremely difficult and requires meticulous dissection and expertise. Detecting lesions, including traction, hyperextension, stretching, and the breech-lower cervical cord, is crucial. All of them have a particular significance for clinical and forensic issues. In a cephalic delivery, from the medulla caudad to the third vertebral body has to be dissected carefully to look for spinal cord injury. The use of rotational forceps has been observed to produce some of the most common spinal injuries by several royal colleges of pathologists (United Kingdom, Canada, Australia, and New Zealand) and the College of American Pathologists.[38,39] Professional bodies regularly issue guidelines for autopsy investigation of fetal and perinatal death to unify autopsy procedures and investigation in pediatric pathology units.[40–44]

Histology

Histologic findings presuppose a complete collection of all organs during the postmortem examination. In case of a postmortem examination with restricted consent to an autopsy, it should be made clear to the clinicians and family that limiting the number of tissues collected could be insufficient to give the cause of death or comment on inheritable diseases.[45] The histologic investigation of fetal or neonatal tissues differs from that of adults because the fetus has no formed organs and needs embryologic skills (►**Figs. 2c–h**, **3**, and **4**). If infants are correctly conserved in cold rooms at the morgue, they may show preserved histology with minimal autolysis. This phenomenon is particularly evident when comparing fetal histology to the histology seen after a postmortem examination performed on adults, where the maceration of organs and tissue autolysis may proceed faster than in fetuses.

The histological examination of the **lung** may disclose aspiration of amniotic fluid with epithelial squames, meconium, and debris as evidenced using Attwood's stain.[46,47]

In chorioamnionitis, the lungs may be directly infected by inhalation of amniotic fluid, which shows infection (►**Fig. 2c**). However, it is also possible that neutrophils can be inhaled from amniotic fluid in the absence of a real bacterial infection.[48–50] In stillbirths or infants who died shortly after birth at an extremely immature stage of development before 26 weeks of gestation, the lungs show a uniform infiltration of neutrophilic granulocytes throughout the airways and airspaces. A marked proliferation of peribronchial lymphoid aggregates indicates infection some days or weeks before birth, as may occur in some cases of amniotic infection. The proliferation of peribronchial lymphoid aggregates means antigenic stimulation. The human fetus may undertake gasping respirations and inhale amniotic fluid

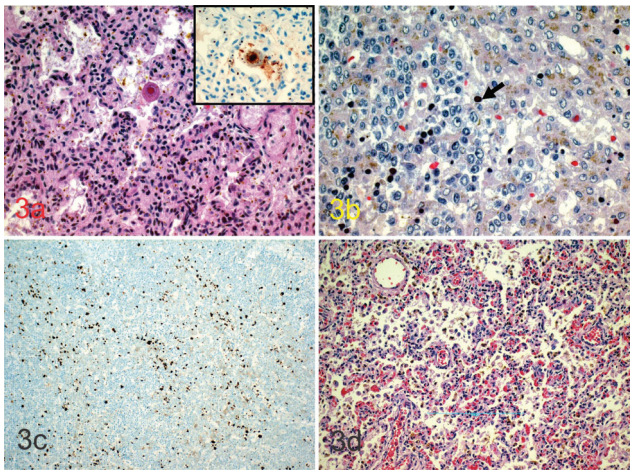

Fig. 3 (**a**) Owl-eye cell in the lung of a stillborn infant. This feature is characteristic of f infection (hematoxylin an eosin staining, 400×). The inset picture shows positive immunohistochemical detection of cytomegalovirus. (**b**) The liver of a stillborn infant with nucleated erythroid precursors (fetal hepatic hematopoiesis) showing nuclear inclusions (*arrow*). The hepatocytes are not affected (hematoxylin and eosin staining, 400×). (**c**) Immunohistochemical detection of parvovirus B19 in the same liver as shown in (**b**), 100×. (**d**) Infantile *Citrobacter* pneumonia of an infant with CHARGE syndrome (C: coloboma; H: heart defect; A: atresia of the choanae; R: retardation of psychomotor type; G: genital anomalies; E: ear abnormalities; hematoxylin and eosin staining, 200×). The *CHD7* gene of CHARGE syndrome (before gene location the term CHARGE association was used for these children with these anomalies) has been found and is located on chromosome 8.

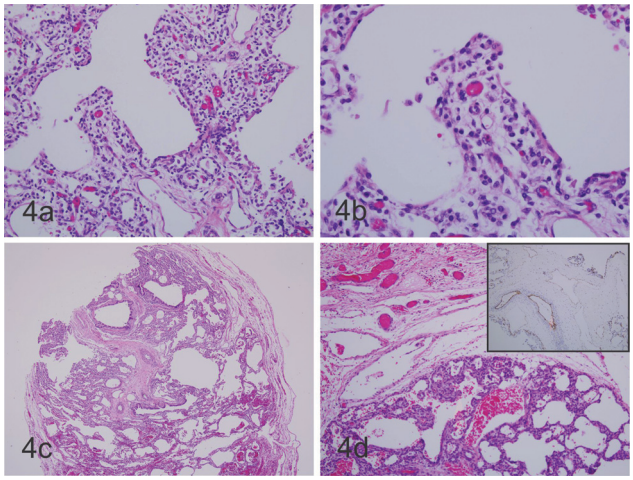

Fig. 4 (**a**,**b**) Alveolar capillaries are significantly diminished in number and are centrally placed within the alveolar septa, several cell thicknesses away from the pneumocyte-lined air spaces in alveolar capillary dysplasia. (**c**,**d**) Lung tissue in cases of congenital pulmonary lymphangiectasia with dilated lymphatic channels without lymphatic proliferation. Inset: CD31 immunohistochemical stain in a case of congenital pulmonary lymphangiectasia highlighting dilated lymphatic spaces. The positive CD31 stain in the endothelial lining confirms that the dilated spaces are lymphatic in origin, not artifacts.

with squames and meconium if this has been passed in the amniotic fluid.[51–53] Therefore, disclosing these findings in the postmortem investigation report is imperative. Histology examination may also reveal infection with viruses with pathogenesis during intrauterine life. They include adenovirus, cytomegalovirus (CMV), and parvovirus, among others. Ancillary studies, including immunohistochemistry, molecular biology, and viral culture, are needed to confirm the presence of cytopathic effects from the viruses.[11,54] Lung tissue is precious because it may show the characteristic features of an intrauterine infection when autolytic changes have hidden the histology of other internal organs. It is of note that in survivor babies that die a few days after birth (early neonatal death), inhaled epithelial squames often persist for many weeks and may be the cause or the triggering factor for a sepsis cascade (►**Fig. 2d**).[55,56] Surfactant replacement therapy is an effective and often life-saving treatment for newborn infants with respiratory distress syndrome (RDS). Since the pioneering efforts of Fujiwara and colleagues in the 1980s,[57] numerous clinical trials have demonstrated the efficacy of exogenous surfactant in improving the compliance of the lung, decreasing requirements for inspired oxygen, improving oxygenation, reducing the incidence of air-leak complications, and increasing survival.[58] Moreover, the pathologist can encounter hemorrhage with extravasations of erythrocytes in the interstitial space and alveoli, hyaline membranes, evidence of persistence of fetal circulation with thick muscular and adventitial layers due to the maintenance of a fetal-type high pulmonary vascular resistance, and evidence of congenital pneumonia with neutrophilic granulocytes in the lumen of the pulmonary tree. Histologic examination of the lung tissue may reveal abnormal vascular development, such as in alveolar capillary dysplasia, leading to nonfunctional air–blood interfaces (►**Fig. 4**). Alveolar capillary dysplasia is a cause of respiratory distress, persistent pulmonary hypertension, and early neonatal death. Failure of the pulmonary interstitial connective tissues to regress in the 5th month of fetal life leads to the dilation of pulmonary lymphatic vessels, as seen in the congenital form of pulmonary lymphangiectasia (►**Fig. 4**).

Examining both **kidneys** helps identify acute tubular ischemic necrosis, acute tubular toxic necrosis, or papillary necrosis. For example, focal necrosis with loss of nuclear staining in proximal tubules might be interpreted as an autolytic change, but an accompanying interstitial hemorrhage indicates that this is an early stage of renal cortical necrosis. Moreover, the thickness of the glomerulogenic zone and its ratio to the definitive zone are very helpful in assessing renal maturity (►**Fig. 2e**). While tubules may deteriorate within 48 to 96 hours, renal maturity can still be easily assessed by counting the number of ranks of glomeruli beneath the glomerulogenic zone.[59]

The histological examination of the **heart** is essential. Hypoxia may be revealed by hypereosinophilia of the myocardial fibers. Subtle evidence of hypoxia is standard, with rates up to 20%.[60] Moreover, inflammatory causes may be quickly ruled out. Several viruses may infect the heart with developing intrauterine myocarditis.[61] An alteration of the constitution of the myocardial tissue may occur in case of metabolic disease and alteration of cardiac conduction tissue

damage. Acute myocardial necrosis can be observed occasionally in a few infants who survived for days or weeks on ventilators and in fetuses with trisomy 13 syndrome.

- Effects of chronic stress can be detected in the **thymus**, where there is a loss of cortical lymphocytes. The van Baarlen Index may be used to assess fetal distress.[62] Some lymphophagocytosis in the cortex characterize grade 1; in grade 2, there is a starry-sky pattern with some shrinking of the cortex and separation of the thymic lobules; in the histology of the thymus from patients with grade 3, there is blurred corticomedullary demarcation, advanced lymphophagocytosis, and narrowing of the cortex and increased separation of thymic lobules. Finally, grade 4 is characterized by pronounced lymphocytic depletion of the cortex with reversed density, that is, more lymphocytes in the medulla than in the cortex, prominent interstitium and vessels, advanced shrinking, and separation of the thymic lobules.
- The **liver** needs a careful investigation to exclude malformation of the ductal plate and fibrocystic diseases.[63–68] The study of extramedullary hematopoiesis is essential to assess fetal maturation, infection, and congenital abnormalities of the intrahepatic biliary system.[67,69] Oil red O and Sudan staining are crucial to identify metabolic diseases and must be performed routinely on frozen liver sections.[15,16]
- The **spleen** may be key in some settings. Examination of the spleen is often limited due to autolysis, but extramedullary hematopoiesis may still be revealed on optimally stained tissue sections. The nuclei of such cells often appear more hyperchromatic relative to the background spleen. Moreover, sickled red blood cells, Gamna–Gandy bodies, and infarcts may be seen in the spleen in the setting of some hematological diseases (e.g., sickle cell disease). Hemophagocytosis may also be identified in the spleen as part of a primary or secondary hemophagocytic lymphohistiocytosis disorder.[70]
- The examination of the **adrenal** tissue can accurately disclose the timing of death.[71,72] Using oil red O and Sudan staining, the distribution of adrenal cortical lipids may be correlated with the duration of fetal distress preceding intrauterine death in fresh and macerated stillborn infants. In new stillborn infants, acute asphyxia is associated with diffuse lipid depletion. In contrast, chronic distress is associated with lipid depletion of the superficial fetal cortex and sparing of the deep fetal cortex. In macerated stillborn fetuses, three patterns have been recognized. Type 1 is characterized by the confinement of lipids to the adult cortex, while in type 2, lipids are present throughout the fetal cortex. In type 3, there is massive fatty change throughout the fetal cortex. It has been declared that type 1 change is associated with an acute mode of death and type 2 with a more prolonged illness. In contrast, type 3 has been associated with chronic illnesses, for example, preeclampsia and placental infarction. Other characteristic features recognizable in fresh stillborn infants include a diffuse compact cell change, increased pyroninophilia of the cortical cells, and degeneration with or without cytolysis of the cortical cells. In preterm infants, there is a cystic pseudofollicular change of the definitive cortex due to focal degeneration of the adrenal cortical cells (►**Fig. 2f**). This pattern has also been associated with prenatal stress.[73]
- Necrotizing enterocolitis may be found in the examination of the **bowel**.
- Irregularity of the **osteochondral junction** of the rib may indicate prenatal stress.
- The study of the skin is useful to diagnose neonatal genodermatosis (►**Fig. 2g, h**) or other cutaneous diseases and to determine the skin's maturity.[74] **Brain** tissue examination may show old damage found in 44% of stillbirths and ~20% of early neonatal deaths, particularly in the occipital white matter.[75] An essential element to consider is that signs of intrapartum damage take up to 48 hours to develop fully. Apoptosis does not seem to be a significant factor in the brain damage of preterm babies, except for infection.[76,77]

Immunohistochemistry allows the determination of the cellular origin of poorly differentiated tumors and has acquired a wide range of applications in diagnostic pathology. The most common applications include the determination of the cellular origin of poorly differentiated tumors or the confirmation of the specified cellular origin in well-differentiated or moderately differentiated tumors, the classification of hematolymphoid diseases, the detection of micrometastases in tissue, the identification and qualitative estimation of hormone receptors and prognostic markers in tumors, the evaluation of cell cycle activity, and the detection of viral and other infective agent antigens, for example, CMV, parvovirus B19, herpes virus simplex, *Legionella pneumophila*.[11] In particular, some markers may be useful for the development stage of lung and renal differentiation. Thyroid transcription factor-1 (TTF-1) is crucial during the lung development. Throughout gestation, TTF-1 nuclear staining is demonstrated in airways abutting pleural, peribronchial, or perivascular connective tissue, despite being less prominent in the centers of lobules. By 23 weeks, many cells in cuboidal but not columnar cell-lined airways show labeling of their nuclei. At term, TTF-1 is identified mostly in type II epithelial cells. In hyaline membrane disease, little or no TTF-1 is recognized except in open terminal airways, while in lungs of infants affected with bronchopulmonary dysplasia, TTF-1 was absent in areas of alveolar collapse or infection, but it was present in regenerating open airways. It also seems that the temporospatial distribution of TTF-1 follows patterns of distribution of surfactant protein B in developing and pathological lungs.[78] Renal tubular dysgenesis relies on the immunohistochemical confirmation involving the antiepithelial membrane antigen (EMA) and the antibody against the hematolymphoid antigene cluster of differentiation 15 (CD15) as immunohistochemical markers. EMA is a marker for distal and collecting tubules and anti-CD15 identifies an early myeloid differentiation antigen and is a marker for proximal tubules.[79] Similarly, molecular pathology may

increasingly play a major role during the stillbirth investigation. Next-generation sequencing (NGS) and nanopore sequencing may play a major role on the platform of thorough investigation of the etiology of fetal death. In particular, these techniques can be implemented in several laboratory information systems.[5]

Placenta

The placental examination is essential and is necessary (1) to demystify the "placental insufficiency" concept and (2) use evidence-based guidelines in investigating and interpreting placental lesions (►**Fig. 5**). The impact of extremely preterm births on perinatal mortality rates and health costs is substantial, and the term "placental insufficiency" has been misused for a long time and may be misleading if the underlying placental condition is not diagnosed.[80] Currently, guidelines, standards, and directives about placenta diagnostics benefit clinicians and pathologists in clinical practice and those facing litigation.[81–84] The following section does not aim to be comprehensive of all placental lesions that could be associated with intrauterine fetal death and/or FGR but tries to illustrate the most important diagnoses that can be encountered in pathology following a request for a placental examination.

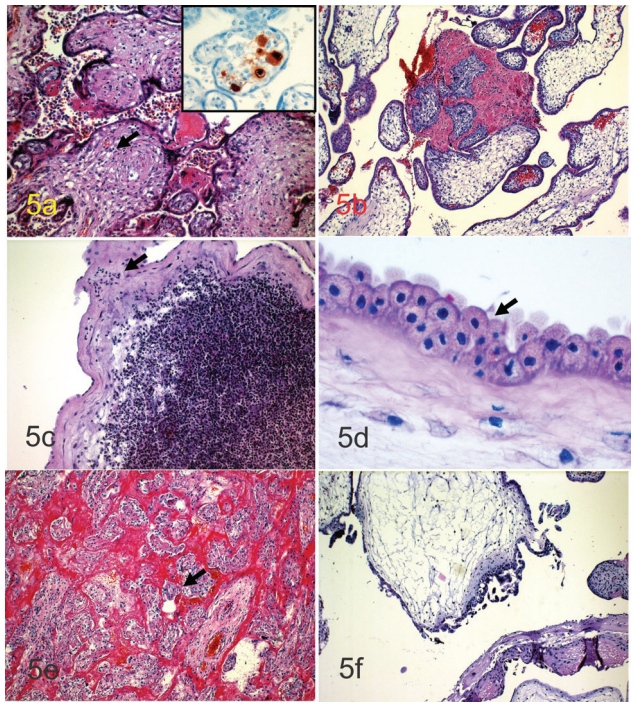

Fig. 5 (**a**) Plasma cell infiltration of the intervillous space (*arrow*) due to cytomegalovirus infection (hematoxylin and eosin staining, 200×). Inset: Cytomegalovirus detection by immunohistochemistry. (**b**) Perivillitis with encircling of small villi by fibrin and neutrophilic granulocytes (*arrow*; hematoxylin and eosin staining, 200×). (**c**) Marked necrotizing chorioamnionitis with infiltration of the subepithelial tissue (*arrow*; hematoxylin and eosin staining, 200×). (**d**) Amniotic epithelium change (vacuolation, *arrow*) associated with omphalocele of the baby (hematoxylin and eosin staining, 400×). (**e**) Massive intervillous fibrin deposition (*arrow*; hematoxylin and eosin staining, 100×). (**f**) Syncytiotrophoblastic hyperplasia (*arrow*) in pregnancy with triploidy (hematoxylin and eosin staining, 100×).

One of the most important findings is **placental abruption**, which is the early separation of a healthy placenta from the uterine wall before delivery. It is appropriate to consider that in two-thirds of cases, placental abruption is not evident during the examination of the placenta. In this sense, it is vital to get the whole history of the pregnancy and examine the fetus that may show marked petechiae because of compression of placental vasculature by hematoma. Particular attention should be given to the cord, especially to the insertion, presence of true knots, nuchal cord, prolapsed cord, and short cord, among others. It is essential to look for evidence of the nuchal cord with signs of strangulation around the neck. A critical review of the evidence supported by additional pathological findings such as one-sided congestion and thrombosis is essential. Placental diagnostics is further complicated by the presence of fetomaternal hemorrhage and tumors, which can also add some challenges in the determination of placental hemorrhage and definitely intrauterine fetal death. Hemorrhages can be marginal or retroplacental intervillous thrombi and acute parenchymal hemorrhages. The data that not all retroplacental hemorrhages are abruptions rely on the concept that abruption is defined as an antenatal detachment of the placenta, which is clinically significant. The etiology of placental abruption entails maternal vascular disease (preeclampsia, hypertension, thrombophilias, and autoimmune diseases), trauma, uterine anomalies, placenta previa, multiparity substance abuse (e.g., cocaine and nicotine), folic acid deficiency, and status post amniocentesis. The incidence of placental abruption seems to be ~1 to 4% of all deliveries, but this rate may be significantly higher if we consider the hidden abruption (*abruptio placentae occultum*) or when the clinical criteria of significance are reconsidered. Finally, an acute retroplacental hemorrhage, which occurs less than an hour before delivery, is considered to be indistinguishable from normal postpartum blood clot. The underlying placental parenchyma may reveal placental compression, necrosis, and/or acute inflammation. Moreover, there is hemosiderin accumulation (4–5 days) and increased perivillous fibrin deposition due to the RBC breakdown. Other data suggestive of maternal vascular underperfusion should be screened.

Infection may masquerade as asphyxia. Pregnancy-associated infections can take place either ascending (generally bacterial) infections from the vagina or cervix area or hematogenously from the maternal circulation. This setting occurs often with TORCH pathogens, *Listeria monocytogenes*, *Fusobacterium nucleatum*, and other rare microorganisms.

The current Amsterdam Placental Workshop Group Consensus Statement[85] includes Staging and Grading of the Maternal and Fetal Inflammatory Responses in Ascending Intra-Uterine Infection subdivided as Fetal Inflammatory Response and Maternal Inflammatory Response. The Fetal Inflammatory Response has three stages (stage 1: chorionic vasculitis or umbilical phlebitis; stage 2: involvement of the umbilical vein and one or more umbilical arteries; and stage

3: necrotizing funisitis) and two grades (grade 1: not severe as defined and grade 2: severe—near-confluent intramural PMN leukocytes with attenuation of vascular smooth muscle).[85] The Maternal Inflammatory Response also includes three stages (stage 1: acute chorionitis or subchorionitis; stage 2: acute chorioamnionitis with extension of the PMN leukocytes into fibrous chorion and/or amnion; stage 3: necrotizing chorioamnionitis revealing karyorrhexis of PMN leukocytes, amniocyte necrosis, and/or amnion basement membrane hypereosinophilia) and two grades (grade 1: not severe as defined and grade 2: severe—confluent polymorphonuclear leukocytes or with microabscesses at subchorionic level subchorionic). These stages of maternal inflammatory response have been estimated, at least partially, to be associated with the duration of infection. If microabscesses are encountered, it is wise to perform a periodic acid–Schiff (PAS) or Grocott's methenamine silver (GMS) stain to identify a fungal participation.[86] There are early (first week) and late (2nd–4th week) neonatal sepsis cases with babies that may be initially well and then rapidly decline hours or days after birth. The infection is usually acquired during labor (enteropharyngeal organisms). The bacteria include group B streptococci, *Haemophilus* spp., *Escherichia coli*, and viruses, most commonly herpes simplex type II. CMV may be a significant cause of stillbirth and has to be investigated carefully (►**Fig. 5a**). Most cases of fetal parvovirus B19 infection occur in early or mid-gestation when nucleated precursors of the erythrocyte line are most numerous. However, some stillborn infants can also be found positive for parvovirus B19 (►**Fig. 5b, c**), but not all affected infants are conspicuously hydropic. Indeed, the possibility of parvovirus infection should be considered in any case of intrauterine fetal death.[11] Immunohistochemistry can be used to confirm the histopathologic diagnosis and may be of particular help where there is advanced organ maceration and tissue autolysis, particularly with fetal demise, which can occur even in one fetus of a twin pregnancy.[11,87] It has been stated that microbiology screening of all stillborn infants is not a good use of resources, and bacterial or viral cultures should be performed only in the cases where gross examination indicates the probability of infection.[88] Conversely, we think microbiology investigation is vital in investigating perinatal death. The infection can provide valuable information in preterm infants or newborns with congenital malformations (►**Fig. 5d**). Indeed, the Royal College of Pathologists of the United Kingdom scores microbiology investigation in evaluating the adequacy, correctness, and completeness of perinatal postmortem examinations.[89]

Chronic villitis is chronic inflammation constituted by lymphocytes and histiocytes with or without plasma cells involving the chorionic villi. There are two broad categories based on etiology. Chronic villitis can be induced by microorganisms or villitis of unknown etiology (VUE). Chronic villitis is found in ~10 to 15% of all placentas. Infectious causes of chronic villitis are usually TORCH infections (e.g., CMV). Chronic intervillositis without villitis is often encountered in infection due to *Placenta falciparum* (malaria) and *Borrelia burgdorferi* (Lyme disease). VUE accounts for more than 95% of chronic villitis. It is substantially defined by the lack of a clear cause. Most of these placentas with VUE harbor an alloimmune-mediated villous injury. VUE is encountered with donor oocyte in vitro fertilization (IVF) compared with nondonor IVF. In VUE, there is a nonuniform (multifocal) involvement of the placenta. There is a chronic inflammatory infiltrate of lymphocytes, histiocytes, histiocytic giant cells, and plasma cells, which is used to subclassify VUE into low- and high-grade villitis based on the number of involved villi. In fact, the presence of up to 9 or less than 10 villi per cluster affected by inflammation categorizes the VUE as low grade, but the occurrence of more than 10 villi per cluster is labeled as high-grade VUE. There is also a stage associated with multifocality. VUE is focal when only one slide is involved, but VUE is multifocal when it occurs in more than one slide. Chronic chorioamnionitis is the most common placental lesion in late preterm birth. It is associated with an increase in the incidence of VUE in this population.[85,86]

In **massive perivillous fibrin deposition** (MPVFD), there is markedly increased perivillous fibrin and extracellular matrix fibrinoid surrounding the distal villi in the lower two-thirds of the placenta parenchyma. MPVFD is in a continuum with maternal floor infarction (MFI), usually including the basal plate. MPVFD is a rare disorder that affects 0.03 to 0.5% of baby deliveries. Although the etiology for MPVFD remains unclarified, it can recur in future pregnancies with a variable range of 12 to 78%.[86] MPVFD can occur more often in patients with autoimmune diseases, thrombophilias, preeclampsia/maternal hypertension, long-chain 3-hydroxy acyl-CoA (LCHAD) deficiency or mutations, and in patients with an imbalance in angiogenic and antiangiogenic factors. MPVFD can also be found in fetuses with renal tubular dysgenesis, FGR, and oligohydramnios. Perivillous fibrin occupying >30 to 50% of the intervillous space has been indicated to be potentially lethal to the fetus. A semiquantitative scoring system has been proposed by Katzman and Genest for making the diagnosis of MPVFD. A classic pattern is defined by the basal villous involvement by fibrinoid along the entire maternal floor and of >3 mm thickness on at least one slide. The transmural MPVFD entails more than 50% of villi encased by fibrinoid material with a transmural extension on at least one slide, while the borderline MPVFD involves an encasement of 25 to 50% of villi in a transmural distribution on at least one slide.[10,85,90]

Finally, two important aspects that need to be tackled in a placenta pathology report is the presence of features suggesting maternal vascular malperfusion and/or fetal vascular malperfusion. There is plenty of placenta atlas illustrating the findings of these two main categories, and we remind the reader of these definitive texts. However, we would like to summarize that features of fetal vascular malperfusion include avascular villi, villous stromal-vascular karyorrhexis, stem vessel obliteration, intramural fibrin deposition, thrombosis, and vascular ectasia, while features of maternal vascular malperfusion include infarcts, retroplacental hemorrhage, distal villous hypoplasia, accelerated villous maturation, chorangiosis, and decidual arteriopathy. In ►**Table 1**,

Table 1 Minimal data set–based placenta pathology report

Placenta, umbilical cord, and fetal membranes, birth:
• Singleton/twin placenta (-chorionic/-amniotic), weight small/adequate/increased for the indicated gestational age of … weeks (… g, …–… g, 10th–90th P)
• Fetal inflammatory response (stage #, grade #)/ three-vessel umbilical cord, … inserted, histologically within normal limits
• Maternal inflammatory response with chorioamnionitis (stage #, grade #)/fetal membranes, …-inserted, histologically within normal limits
• Placental disc with third trimester villi with
Features of fetal vascular malperfusion: avascular villi, villous stromal-vascular karyorrhexis, stem vessel obliteration, intramural fibrin deposition, thrombosis, and vascular ectasia
Features of maternal vascular malperfusion: infarcts, retroplacental hemorrhage, distal villous hypoplasia, accelerated villous maturation, chorangiosis, and decidual arteriopathy
No/yes villitis of unknown etiology
No/yes histologic evidence of decidual arteriopathy

Notes: G, grams; 10th–90th P, 10th–90th percentile.

the minimal data set–based typical placenta pathology report is depicted.

Discussion and Conclusion

Overall, there are evidence-based data for sustaining a high clinical autopsy rate. These may include timely communication of autopsy findings to clinicians, the use of autopsy data in institutional risk management/reduction, the emphasis to quality control benefits of the unexpected conclusions to family members, training in the seeking of consent for autopsy, effective organization, management, and integration of all aspects of the autopsy service. There are modern technologies targeting the approach to minimal invasive autopsy (e.g., endoscopy) or noninvasive autopsy (magnetic resonance imaging or computer tomography based) that should find room in our institutions approaching the first quarter of the 21st century.[91–96] Such tools should be promoted for both clinical and research purposes.

Perinatal death is a complicated and emotionally challenging entity for all involved parties. Pathologic examination in cases of perinatal death requires an accurate and precise approach that a skilled, observant pathologist can provide, ideally one with pediatric/perinatal expertise. Because the examination of perinatal death may be very challenging and the examination may last several hours, the examiner needs to compare the findings with standard and near-normal findings, a skill that is enhanced with increasing experience and appropriate workload measures that have been difficult to set up.[97] Postmortem investigation is not a technique of the past because Fanconi, who is probably one of the best known pediatricians, had a profound knowledge of pathology because he spent time studying this discipline. In the 21st century, pediatrics is transforming, and pediatric pathology will help discover new diseases and identify responses to treatments in infants and children.[98] The autopsy has significant potential and is an important technique to discover the unknown and confirm or refute clinical suspicions. Here, we should recall the Latin motto "*Hic locus est ubi mors gaudet succurrere vitae*," which is commonly translated as: "This is the place where death delights in helping life." This saying has been attributed to Giovanni Morgagni, one of the most famous anatomists and pathologists who lived in the 18th century. This saying has been mentioned worldwide and said to be copied on the door headers, above transom windows, or simply on the walls of several dissection rooms following the enactment of the Murder Act (1751–1973), an act of the Parliament of Great Britain and Ireland. Numerous pediatric pathologists have been involved in both forensic and clinical adult autopsy cases for several years, and the involvement of laboratory physicians in debriefing families and relatives is critical for the future of this subdiscipline.[3,4]

Author Contribution

C.M.S. was responsible for project development, data collection, and manuscript writing. D.S. and T.A.J. were responsible for data collection and manuscript writing. All the authors reviewed the manuscript and approved it before submission.

Conflict of Interest

None declared.

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