Forensic Aspects of Perinatal Deaths

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ABSTRACT

From a forensic pathologist's perspective, there are several aspects of the perinatal postmortem that are particularly important. If a fetus is found abandoned, the pathologist needs to ascertain the fetal age, the appropriateness of growth, if the baby was born alive or dead, and the possible causes of death. In cases of litigation for perinatal deaths occurring in hospitals, access to the obstetric and neonatal notes (if the baby is born alive and dies a few hours or days later) is fundamental to reach a correct interpretation and conclusion. The most important points to consider in cases of intrapartum death are the roles of asphyxia and trauma in the causation of the baby's death. Timing of the fetal death in relation to delivery may also be an important point in these cases. Finally, intrapartum lesions should always be considered in the differential diagnosis of possible child abuse in babies aged two months or less. *Acad Forensic Pathol.* 2018 8(3): 452-491

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INTRODUCTION

Assessing at autopsy whether an infant was alive at the time of delivery may be difficult, particularly if there has been a delay in retrieving the body, or if it has been affected by the environment (i.e., temperature, water immersion, damaged by predatory fauna, etc.). Several factors should be considered at autopsy when assessing the probability that a baby has been born alive, including: degree of maceration, gestational age, fetal growth, presence of congenital abnormalities, histological and microbiological evidence of infection, and significant placental abnormalities (if it is available for examination). If there is no decomposition, identifying air in the lungs, middle ears, or stomach may also be an indication of a live birth (1). Postmortem imaging can be extremely useful in providing guidance (see below under radiology) (2). Although the features described above may be helpful, they are influenced by postmortem changes. Therefore, a positive flotation test or a positive radiographic finding should be interpreted with caution, as air may be introduced into the lungs or stomach during cardiopulmonary resuscitation, secondary to decomposition, and/or postmortem overgrowth of gas-producing organisms. Similarly, lungs sinking in water may represent a false negative result, as it may happen with lungs with severe bronchopneumonia or hyaline membrane disease. Careful clinical-pathological correlation and scene investigation is therefore recommended in all cases (3).

This article will address autopsy, developmental, macroscopic, and histologic features that can help the forensic pathologist to estimate 1) fetal age; 2) time elapsed between intrauterine death and delivery; 3) stillbirth versus born alive; and 4) common causes of perinatal death.

DISCUSSION

Estimation of Fetal Age

At External Examination

Weights and Measurements

In any perinatal postmortem, the external examination includes recording the body weight and external measurements. These should be compared against appropriate gestation-related normal values, which preferably should be customized to maternal ethnicity and country (4). Standard measurements include crown-rump (CR), crown-heel (CH), head circumference, and foot length; additionally, thoracic circumference (at the level of the nipples) and abdominal circumference (at the level of the umbilicus) may be helpful to compare with measurements taken by ultrasound and to help estimation of the gestational age. Foot length is the most reliable external measurement in the assessment of gestational age, even if the fetus is macerated (4). All lengths should be determined to the nearest 0.5 cm (2, 4). Normally, the CR length in the fetus and newborn is approximately two thirds of the CH length, and the head circumference and CR length should not differ more than 1 cm or so (2).

During dissection of the organs, the weight of each one should be taken using scales accurate to 0.1 g. The organ's weight should be recorded in the autopsy report, along with expected values (2).

Radiology

Full skeletal radiology should be part of the fetal, neonatal, and infant postmortem examination. Ideally, the report should be issued by a radiologist with expertise in fetal and pediatric imaging. The developmental stage of ossification centers constitutes a useful resource in the estimation of fetal age. In viable fetuses, the relevant ossification centers are: greater cornua of hyoid bone (28-32 weeks); 5th cervical vertebrae costal process (32-36 weeks); 2nd, 3rd, and 4th cervical vertebrae costal processes and coccyx (37-40 weeks); distal femur epiphysis (35-40 weeks); proximal tib-

ia epiphysis (40 weeks), talus (24-32 weeks); middle 4th phalange (29-32 weeks); and middle 5th phalange (33-36 weeks) (2, 5). If using a digital faxitron, the length of the femur and the humerus compared with appropriate tables will also help to establish fetal age (6). Imaging is a useful aid to determine if a baby had been stillborn or liveborn. In the absence of putrefaction, the presence of air in the lungs, stomach, and intestine, better assessed with magnetic resonance imaging (MRI) or computed tomography (CT), is a sign of livebirth (7, 8). On MRI, the presence of air in the lungs has the highest accuracy when compared to the traditional autopsy (92.9%) (7). Similarly, postmortem multislice CT demonstrates the extent of aeration of the peripheral alveoli, thus making it a useful tool in the possible differentiation between naturally and artificially aerated lungs (8).

Intrauterine Growth Restriction

The term intrauterine growth restriction (IUGR) refers to a fetus that has not achieved its optimal growth for its gestational age. There is a growing interest in assessing IUGR using customized growth charts based on maternal ethnicity, the country of birth, and the maternal characteristics (9). The presence of IUGR in a fetus may have clinical relevance to the cause of the stillbirth. In addition, the condition causing IUGR may recur in future pregnancies, requiring close clinical monitoring (9).

Intrauterine growth restriction can be symmetrical or asymmetrical. Symmetrical IUGR (also known as “reduced growth potential”) is related to conditions affecting the fetus at an early developmental stage (i.e., genetic conditions or congenital infections). In these cases, the whole body, including the brain, is small and there is preservation of the brain: liver ratio (normal ratio: 2.5-3.1:1) (10). Asymmetric IUGR is commonly related to conditions affecting the fetus at a later stage of development, usually related to uteroplacental factors. In asymmetric IUGR (also termed nutritional IUGR), the brain volume is better preserved than any other organ, especially the liver, leading to an increase in the brain: liver ratio (>3.1:1; or >4:1 in the macerated fetus). The fetus affected by

nutritional restriction is “tall and thin,” with a large head, dry skin, and thin thighs (4). These features are more noticeable at or near term.

The following features are considered normal at post-mortem examination (9, 11): 1) fetal weight between 10-90th percentile of a given population adjusted for race, gender, and gestational age; 2) appropriate subcutaneous tissue (after 24-25 weeks gestation); 3) normal brain: liver ratio (2.5-3.1:1); 4) placental weight and feto: placental ratio between 10-90th percentile.

Large for Gestational Age

A large for gestational age (LGA) fetus is one whose birth weight is above the 90th percentile for gestational age (9). A large baby may suggest that the mother is diabetic (pre-gestational or gestational diabetes) or that she may develop diabetes in a future pregnancy. It is important not to erroneously diagnose it as a more advanced gestational age. More specific clues pointing to the infant of a diabetic mother include: cherubic face, increased subcutaneous fat in the thorax and abdomen, large liver, a degree of sacral agenesis, beta cell hyperplasia in the pancreas, and, less frequently, eosinophilic insulinitis. Characteristically, the placenta shows delayed villous maturation (**Image 1**).

A fetus of a diabetic mother may show appropriate weight for gestational age. In these cases, the fetus was meant to be large for gestational age but did not achieve its full potential growth, generally due to placental pathology. These fetuses may have been exposed to double stress: the stress of being macrosomic with hyperinsulinism and that of the nutritional restriction (9), and it is often seen when the placenta shows signs of maternal vascular disease.

Histological Features That Help Estimate Fetal Age

Lung Developmental Stages

Development of the lungs goes through four main stages: glandular (5-16 weeks), canalicular (16-24 weeks), saccular (24-35 weeks), and alveolar (35 weeks onwards) (12). During the glandular stage, there

Image 1: Intrauterine death. Large for gestational age fetus showing **A)** large villi with delayed maturation (H&E, x200); and **B)** eosinophilic infiltrates present in a pancreatic Langerhans islet, so called “eosinophilic insulinitis” (H&E, x600).

are branching tubules derived from an endodermal bud lined by columnar epithelium and widely separated by proliferating mesenchyme (**Image 2A**). Later, in the glandular stage, there is condensation of mesenchyme around groups of branches providing an early lobular appearance (**Image 2B**). The canalicular stage is characterized by development of respiratory bronchioles (**Image 2C**). Lung development continues with vascularization of the tubular framework, progressive reduction of the intervening mesenchyme, gradual thinning of the septal walls, and presence of primitive acinar saccules (**Image 2D**). At around week 28 sufficient

alveolar precursors have matured, and differentiation of the alveoli appears around 35 weeks and is characterized by a single alveolar lining at term (**Image 2E**). There is a tenfold increase in the number of alveoli between birth and 24 months of age (12).

Brain Developmental Stages

The normal brain development goes through different stages involving formation of anatomical structures (6-20 weeks), neuronal migration (6-20 weeks), and neuronal differentiation (synaptogenesis: from 11

Image 2A: Lung development, early glandular developmental stage in a 12-weeks gestational age fetus depicting prominent intervening interstitial mesenchyme separating early branching tubules (arrows) (H&E, x200).

weeks, and myelination: from 18 weeks onwards). Macroscopically, the brain gyral development and weight aid in the estimation of fetal age (**Images 3A to E**). Histologically, the stages of neuronal migration and differentiation are the best tools to assess development (**Image 4**) (13). When examining a fetal or neonatal brain, it is important to bear in mind that the patterns of damage are different at different gestational ages. This is particularly useful to assess at which fetal age a term neonate may have suffered brain damage: from 28 to 36 weeks gestation, the main damage is to the white matter and intraventricular hemorrhage. From 36 weeks to term, the main damage occurs in the grey matter in the basal ganglia, the thalamus and the posterior limb of the internal capsule, and in the watershed area of the cortex (13).

Kidney Developmental Stages

The human kidney is organized in lobes, which consist of a medullary pyramid and its cortex. Both elements are formed in the nephrogenic zone, which is easily recognized at low power in all preterm fetuses in the most outer portion of the cortex. The permanent, metanephric kidney begins its formation around four to five weeks (14). The nephrogenic zone starts to decrease after the 30th week and as nephrogenesis ends between 32nd and 36th weeks there is no nephrogenic zone in term babies. As glomeruli develop, they push older glomeruli down into the medulla. In well oriented sections, the number of glomerular layers gives an idea of the fetal age as shown in **Table 1** and **Image 5** (15).

Image 2B: Lung development, late glandular development showing condensation of mesenchyme around groups of branches (arrows), providing an early lobular appearance (H&E, x200).

Image 2C: Lung development, canalicular stage in a 19-weeks gestational age fetus showing respiratory bronchioles (H&E, x100).

Image 2D: Lung development, saccular developmental stage, with vascularization, reduction of the intervening mesenchyme, gradual thinning of the septal walls, and presence of primitive acinar sacculles (H&E, x200).

The oldest or most mature glomeruli are located in the deeper cortex close to the juxta-medullary junction, whereas the newly formed rudimentary glomeruli form a subcapsular layer termed the nephrogenic zone. A previous study looked into the relationship between the period of gestation and the number of glomerular generations assessed by simple regression analysis concluded that the histological assessment of the sequential development of glomeruli in the fetal kidney can be used as a reliable method of estimating gestational age ($p < 0.0001$) (16).

Time Elapsed Between Intrauterine Death and Delivery: Intrapartum vs. Intrauterine Death Before Labor

In all cases of fetal death, and particularly in cases of intrapartum death, it is important to establish as accurately as possible when the fetus died in relation to the delivery. As always in pathology, time is not an accurate measure but a window of opportunity. If death occurs less than eight hours before delivery, there will be very few changes in the external appearance. From

Image 2E: Lung development, alveolar stage in a 36-weeks preterm neonate showing single alveolar lining. Note presence of meconium aspiration (arrow) (H&E, x200).

approximately 12 hours onwards, features of maceration will develop according to the length of time the fetus has been dead in utero. This will be accompanied by histological autolysis. However, in fetuses of concealed pregnancies that are found (rather than babies born in hospitals), environmental postpartum changes may make proper interpretation difficult. A nonmacerated or fresh fetus with unexpanded lungs and other features of stillbirth (see below) is almost always the result of an intrapartum death.

Maceration

Maceration is the term applied to degenerative changes that occur to the dead fetus retained in the uterus.

It is typically a sterile, gradual, and progressive process (**Image 6**). The speed of maceration may be accelerated by intrauterine infection (9, 17). A rough estimation of the time of fetal death prior to delivery may be done, always taking into consideration possible modifying environmental factors and the time elapsed between delivery and autopsy. A rough guide to maceration is provided in **Table 2**.

When determining the fetal age of a macerated fetus, the most reliable measurement is the foot length since it is less affected than other measurements. In hospital autopsies, when the fetal age at delivery is generally provided, adjustments should be done according to the length of time the fetus had been dead in uterus. The

Image 3A: Gross examination of the brain and spinal cord in a 17-week gestational age fetus, conducted under water and with the aid of brushes to prevent tissue damage. Note the smooth external surface.

Image 3: B) and C) Gross examination of the brain and spinal cord in a 17-weeks gestational age fetus, conducted under water and with the aid of brushes to prevent tissue damage. Note the smooth external surface and the early development of the Sylvian fissure, which helps dating the brain development (arrow in **B**).

Image 3: Gross examination of the brain in a term fetus after four days fixation in 20% buffer formalin showing normal gyri and sulci, D) coronal view; and E) inferior view.

Image 4: Normal brain histology at 15-weeks gestational age. **A)** Low power (H&E, x100) and **B)** high power (H&E, x200) showing prominent germinal matrix (thick arrow), migrating neuroblast in the white matter (thin arrow), and early cortex (star).

organs also change macroscopically with maceration, eventually all being of a similar color after approximately three days intrauterine death (IUD). Some organs are more friable than others, particularly the liver and brain. For this reason, it is advisable to deliver the fetal brain in water, which will support the soft brain while being dissected (**Images 3 and 7**). The presence of bloody fluid in the pericardium and the pleura in particular should not prompt the diagnosis of fetal hydrops, as this is a common occurrence in all IUD of more than two days. Combining the maceration features with the tissue autolysis helps to determine the gestational age at which the fetus died.

Autolysis

Autolysis is the breakdown of tissue by action of enzymes within the cells and is seen in dying or dead cells. Histologically, it is seen as the loss of nuclear basophilia and is related to the loss of DNA. The rate of autolysis varies in different tissues and this helps to determine the probable time of death (**Table 3**) (18). The postmortem interval and the conditions in which the body was kept will also have an effect on tissue autolysis. Autolysis due to IUD should be distinguished from that due to postmortem delay. This is particularly important in the kidney with possible acute tubular necrosis (ATN). In our experience and that of others (19), this differentiation is possible, un-

Table 1: Development of Glomeruli During Gestation (Modified from 15)

Gestational Age in Weeks	Rows of Glomeruli
23 or less	3
24	5-7
28	8-9
32	9-10
36	10-14

less the autolysis is advanced. Acute tubular necrosis is best identified in the proximal renal tubules. The epithelial cells characteristically show a bright pink color in the cytoplasm with loss of nuclear staining (**Image 8A**). In any case, the use of immunohistochemistry with C9 can help to highlight the necrotic cells (**Image 8B**) (20).

If the placenta is available for examination, it can also contribute to assessing the time of fetal death. After 6-24 hours IUD, the placenta will show intravascular karyorrhexis and after approximately two days there will be hemorrhagic endovasculosis (care should be taken distinguishing these changes from thrombi recanalization, which may be similar in a fresh stillborn). The trophoblast basement layer thickens and becomes

Table 2: Approximate Guide to Maceration Timing (Modified from 9)

0-6 hours	Little change, clear corneas
6 h-1 day	Skin peeling on periphery and bony prominences
1-2 days	Widespread skin peeling, abdomen discoloration
2-3 days	Diffuse reddening, hemolytic changes in cord, serosanguinous fluid in body cavities, uniform coloration of organs
4-7 days	Overlapping skull bones, sunken eyes, mobile mandible suture, periosteum and dura lifts from skull bones
>7 days	Brown discoloration
10-12 days	Increased loss of fluid. After many weeks fetus papyraceous

Image 5: Kidney at 19-weeks gestation showing four rows of glomeruli. Also, tubules (arrow) and glomeruli (star) are seen in a subcapsular location (H&E, x100). The line highlights the nephrogenic area.

Image 6: 37-weeks gestational age fetus after **A)** less than eight hours of intrauterine death; and **B)** 24-48 hours of intrauterine death. In both instances, note the red discoloration of the umbilical cord.

Image 7: Removal of the brain in the fetus is facilitated if using a posterior approach. Removal under water supports the soft brain while being dissected.

Image 8: A) Kidney of a stillborn fetus. Note the bright pink appearance of the tubular epithelium with acute tubular necrosis (arrows) (H&E, x400); **B)** immunohistochemistry with C9 highlights the necrotic tubular epithelium in the same case (arrows) (x400).

Table 3: Timing of Autolysis In Relation With the Time Elapsed From Death (Modified from 9)

Loss of Nuclear Basophilia	Tissues (All Timings are Approximate)
4-8 hours	Renal cortical tubules, gastrointestinal tract
24 hours	Liver, cartilage, inner half of myocardium
24-36 hours	Complete in pancreas
48 hours	Glomeruli, outer half of myocardium
72 hours	Complete in liver, definitive adrenals, bronchial epithelium
1 week	Complete in gastrointestinal, adrenals, trachea
2 weeks	Alveolar walls
4 weeks	Complete in kidneys
8 weeks	Complete in lungs and brain

mineralized within five days. Syncytial knots increase after around one week IUD (21, 22). After two weeks, there will be extensive villous fibrosis.

Stillborn vs. Born Alive

The definition of stillbirth recommended by the World Health Organization is a baby born with no signs of life at or after 28 weeks gestation (at or after 24 weeks in the United Kingdom and after 20 weeks in the United States) (23). The major causes of stillbirth include: labor complications, post-term pregnancy, maternal infections (e.g., malaria, syphilis, and HIV), maternal disorders (e.g., especially hypertension, obesity, and diabetes), fetal growth restriction, and congenital abnormalities. Half of stillbirths happen when the woman is in labor (24). Neonaticide is defined as the killing of a newly born infant (less than 24 hours of life) following a live birth (25).

Not unfrequently, the pathologist is required at a perinatal postmortem to determine if the baby was born dead or if it had a separate existence from the mother, and if death was deliberate or due to a perinatal event (1). A “separate existence from the mother” implies that the infant had issued forth from its mother, irrespective of its gestational age, and who breathed or showed any other sign of life after being completely expelled from the maternal passages (even if the child is still attached to the placenta within the mother). The assessment of intrauterine growth and development and the significance of gross and histological findings must be performed by a pathologist with experience in pediatric and perinatal examinations.

In certain circumstances, the pathologist must do an assessment in which a body or body parts of a fetus or newborn are found somewhere, recovered after a home delivery, or the outcome of a concealed pregnancy. Each case should be assessed according to its particular context. Findings suggesting that the baby was stillborn include: maceration (see above), presence of some congenital malformations, or a large retroplacental hematoma (which is associated with a subdural hemorrhage and petechiae on lungs and other viscera and is related to placental abruption leading

to sudden elevation of intracranial pressure—hence the subdural bleeding—and fetal asphyxia) (see **Images 9A to F**) (26). Florid congenital pneumonia with polymorphonuclear leukocytes in the alveoli correlates with chorioamnionitis in the placenta and may be seen both in a stillborn fetus or an early neonatal death. If the placenta is recovered, it should be examined (it is fundamental to record placental weight and measurements) and sampled for histology. In some cases, a thorough perinatal postmortem examination, including a detailed placental examination, fails to identify a relevant condition at death. In these cases, death may be related to cord problems, in particular cord prolapse or compression. The possibility of intrapartum death or a live birth followed by death needs to be contemplated in the event of an unattended delivery (one of the authors [MC] has seen a few cases of teenage mothers giving birth alone following a concealed pregnancy). According to UNICEF, millions of births across the world occur annually without any assistance from a skilled attendant at birth (i.e., medical doctor, nurse, or midwife). Experts agree that the risk of stillbirth or death due to intrapartum-related complication can be reduced by about 20 percent with the presence of a skilled birth attendant (27). The complications and outcomes of unattended delivery were already known in the 1950s and seminal papers were then published both in the UK and in the US (28, 29). A recent systematic review in African countries has demonstrated that skilled delivery attendance is associated with significant reduction of maternal, fetal, and neonatal mortality (30). Unattended delivery has also been included in many stillbirth classification systems (31, 32), and the so-called “Extended Aberdeen” Classification included “unattended delivery” under the category of “unclassifiable or unknown” (28, 30, 32). Keeling states that fetal and perinatal death in the context of unattended delivery can occur in two different settings: either birth may follow a concealed pregnancy, or emergency professional help is unavailable because delivery takes place before skilled staff is available (33). Regardless, unattended deliveries carry a higher mortality than those occurring in the hospital setting (34).

Currently, the legal limit of viability is considered to be around 24 weeks (35). Nonviable infants can also be born alive in unattended circumstances and live for a few minutes or hours (1).

External examination of the lungs is a very useful procedure to seek proof of respiration (36). The lungs of the stillborn are dark, small, and heavy with angular edges and a liver-like appearance. When opening the thorax, the lungs are contracted against the mediastinum (**Image 10**). On cut section, non-aerated lungs show a rubbery consistency, with uniform deep red color and texture. Depending on the length of the respiration period, lungs that have breathed will fill the mediastinum, show a pink or mottled color, and will

have more rounded edges due to expansion. On sectioning, the cut surface appears spongy and there is crepitation on rubbing a slice of lung tissue between the fingers.

A deep red discoloration of the umbilical cord at its fetal insertion is another indication that fetal death has taken place before delivery (**Images 6A and B**) (37, 38).

On the contrary, reddening and desiccation of the cord stump suggests a live birth with a few days survival (**Image 11**) (33). In addition, a clear-cut at the umbilical cord end suggests assisted delivery, whereas a torn end may suggest an unattended delivery. In unattend-

Image 9A: Placental abruption showing a large retroplacental hematoma (arrow) on maternal surface.

ed deliveries (from concealed or known pregnancies), some injuries on the decedent (such as nail marks) may result from the efforts of the mother to help the delivery.

Histological features that aid in the diagnosis of stillbirth can be found in the lungs where uniform alveolar expansion or collapse, polymorphonuclear neutrophils in alveoli, presence of meconium (an amorphous, pale-brown material for which there is no special stain; see below intrapartum asphyxia), and large amount of amniotic debris indicate severe hypoxic stress before birth; and in the umbilical cord vessels where smooth muscle pyknosis, especially at

the periphery, is related to meconium spilling (**Image 12**) (4). The pattern of alveolar expansion varies according to the factor causing the expansion: the uneven dilatation of alveolar ducts and alveoli by air can be distinguished from the uniform dilatation produced by the inhalation of (amniotic) fluid. When the fetus has made strong inspiratory efforts before birth, partial expansion of terminal air spaces may give a saw-tooth pattern (33). If a baby has breathed air for a short time (minutes to few hours), histology will show that the proximal air spaces are proportionally more distended than the distal ones, which show more alveolar collapse (12). Immunohistochemistry is of little practical use in macerated stillbirths.

Image 9B: Placental abruption showing a large retroplacental hematoma (arrows) on cut surface.

The identification of conditions that may have interfered with the fetus' ability to sustain extrauterine life, the presence of signs of intrapartum stress or asphyxia, or coexistence with serious placental abnormalities suggest either stillbirth or intrapartum death due to natural causes. On the contrary, the presence of vital reaction at the umbilical cord stump, gastric contents containing milk (or any extrauterine element), fully expanded lungs, hyaline membranes on histology, and the distribution of lividity may suggest live birth. Samples from the umbilical cord to assess vital reaction should be directed at the boundaries with the

nondesiccated area of the "stump." Polymorphonuclear leucocyte infiltrates are seen in the areas between the mummifying cord stump and the vital tissues of the abdominal wall, forming a demarcation zone (39).

A study has shown that the use of mast cell tryptase, the histiocytic marker CD68, and alpha-1-antichymotrypsin, showed a statistically significant ($p < 0.0001$) different expression in the stillborn and liveborn, suggesting that their expression is useful to identify live birth (40). Of the markers studied by Neri et al., the increased level of mast cell tryptase in umbilical tis-

Image 9C: Placental abruption showing a large retroplacental hematoma on histology (H&E, x100).

sue of liveborn was shown to be the most adequate parameter in the differentiation with stillborn, even if survival has been short (40). Instead, the presence of macrophages in the umbilical cord tissues is dependent of survival time. Hyaline membranes are usually related to prematurity and can take a minimum of six hours to develop and 12 hours to being widespread present in the alveoli (**Image 13**) (41).

Infanticide should be considered and analyzed in the context of the particular circumstances of each case.

The most common methods of infanticide are smothering, strangulation, and head injury. These aspects of perinatal death are beyond the scope of this article, but the face and neck should be carefully inspected in search of injuries, bruises, and/or ligature marks. It should be noted that marks, abrasions, and focal bruising may take place during the extraction process in an unattended delivery and may not indicate inflicted injury, and that petechiae and retinal hemorrhages are very common finding in noncomplicated deliveries (25).

Image 9D: Placental abrasion (arrow) was surrounded by a rim of infarcted villi (star) (H&E, x100).

Common Causes of Perinatal Death: Gross and Histological Aspects

Fetal death may occur before the beginning of labor (antepartum) or during labor (intrapartum). Some babies die in the neonatal period as a consequence of intrapartum asphyxia, trauma, or infection (4).

We discuss here the main causes of intrapartum death and the role of the placenta in antepartum and sometimes intrapartum death.

Intrapartum Trauma vs. Intrapartum Asphyxia

Intrapartum Asphyxia

This occurs when there is impairment of gas exchange during labor, which eventually results in hypoxia, hy-

percapnia, and metabolic acidosis. There are many causes of intrapartum asphyxia that should be considered when investigating intrapartum fetal death (Table 4). During normal labor, the fetus can withstand a temporary degree of asphyxia, which is rapidly reversed between contractions (41). If the effect of the hypoxic insult is maintained, especially if there is metabolic acidosis, there will be changes in most organs, particularly related to capillary damage. There is generalized congestion and small hemorrhages in many organs, particularly in the brain, the falx and tentorium, the lungs, the thymus, and the kidneys; on the heart, petechial hemorrhages tend to be seen along the coronary arteries (42). In many cases, and depending on the duration or the severity of the hypoxia, there will be a thin film subdural hemorrhage arising from the rich plexus in the posterior falx. This is particularly severe in cases of placental abruption due to

Image 9E: A sudden raise in intracranial pressure during abruption caused subdural hemorrhage.

a combination of capillary damage due to hypoxia/acidosis and increased venous pressure (42, 43) (**Image 9**). If the neonate initially survives labor but dies in the immediate neonatal period, the lungs may show intraalveolar squamous cells and meconium (**Image 14**), subpleural and intraalveolar hemorrhages (and sometimes massive lung hemorrhage), and patchy distention due to cardiopulmonary resuscitation; in premature babies, hyaline membrane disease may have developed (**Image 13**). The kidneys may show acute tubular necrosis, which the pathologist should distinguish from postmortem autolysis (19, 20). The thy-

mus may show stress related changes according to the duration of the stress (**Image 15**) (42). The most significant changes, and the ones more helpful to the time of the beginning of hypoxia, are in the brain. **Table 5** shows the approximate timing of different hypoxic brain lesions in term babies. For detailed description of neonatal asphyxia, see reference (13).

Intrapartum Trauma

This includes any physical injury as a consequence of the birth process, some of which may result in death

Image 9F: A sudden raise in intracranial pressure during abruption caused white matter congestion and bleeding (H&E, x100).

Table 4: Causes of Intrapartum Asphyxia (Modified from 41)

Maternal Conditions	Placental Conditions	Umbilical Cord Conditions
Severe anemia	Placental infarction	Abnormal length
Malnutrition	Widespread villitis	Cord entanglement
Chronic renal failure	Villous edema	True knots
Heart disease	Abnormal maturation	Cord prolapse
Peripheral artery disease	Fetal thrombotic vasculopathy	Cord compression
Shock and hypoxia	Prolonged pregnancy	Cord stretching
Maternal hemorrhage	Placenta previa	Cord hematoma
Epilepsy	Vasa previa	Cord tear
Maternal lung disease	Placental abruption	Funisitis
Maternal diabetes	Circumvallate membranes	Vessel thrombosis
Aortic compression	Chorioamnionitis	Vessel aneurysm
Drug abuse	Utero-placental insufficiency	Velamentous insertion
Pregnancy cholestasis		Furcate/marginal insertion
Uterine rupture		Hypercoiled cord
Amniotic fluid embolus		

Table 5: In Utero Survival Time Required To Develop Changes That Help Timing Hypoxic Brain Lesions In Term Babies (Modified from 13)

Feature	Approximate Timing
Axonal injury	< 1 hour
Cell necrosis	5 hours
Cell apoptosis	12 hours
Gliosis	12 hours to 3-6 days
Endothelial thickening	1-2 days
Macrophages	1-3 days
Hemosiderin	2-3 days
Capillary proliferation	7 days
Mineralization	8 days

and are the ones discussed here. Severe birth trauma is now infrequent due to improved obstetric care and most cases are associated with difficult deliveries. Many of the factors that predispose to intrapartum asphyxia increase the risk of birth trauma. Asphyxia itself is a predisposing factor for intrapartum trauma and sometimes it may be difficult to decide whether asphyxia or intrapartum trauma was the main cause of death (42). The other main predisposing factors are instrumental delivery, malpresentation, obstructed or prolonged labor, feto-pelvic disproportion, macrosomia, some fetal abnormalities, and epidural anesthesia. It is important to have detailed obstetric notes available at the time of the autopsy. Prematurity is also a risk factor for trauma. **Table 6** lists the risk factors and the related intrapartum injuries.

When assessing birth trauma, it is important to consider underlying fetal conditions that can mimic in-

flicted trauma, such as connective tissue disorders in lacerations (44), bone disease in fractures (45-47), hematological conditions in bruises and intracranial hemorrhages (48), and the role of asphyxia in the latter (3, 26, 49). Extensive subaponeurotic hemorrhage may cause death due to hypovolemic shock (42, 50).

Another important consideration is the interpretation of birth trauma when the death does not occur shortly after birth. As fractures may be diagnosed at an infant postmortem, some time since birth, it is fundamental not to jump to conclusions. Instead, one should wait until the result of the histology to diagnose abuse, as histological dating of fractures can help to date the fracture (i.e., recent or from birth). It is worth remembering that not only forceps but also vacuum extraction may cause skull fractures, and that they may also rarely occur in normal vaginal deliveries. A careful interpretation of the obstetric notes is mandatory.

Image 10: Concealed pregnancy in a heroin user. Note the deep red, nonexpanded lungs in the fetus, in keeping with stillbirth.

Image 11: Neonatal death due to hydrops and heart malformations. Note the desiccation of the umbilical cord (arrow), in keeping with a period of survival after birth.

Table 6: Risk Factors and Related Intrapartum Injuries (Adapted from 41)

Normal vaginal delivery	Caput succedaneum Cephalhematoma (rare) Skull fractures (rare) Retinal hemorrhage
Precipitate vaginal delivery	Subdural hemorrhage
Malpresentation (including breech)	Bruising and lacerations Occipital osteodiasis Spinal injury
Vacuum (ventouse)	Caput succedaneum Subaponeurotic hemorrhage Skull fractures (rare) Retinal hemorrhage
Forceps	Bruising and lacerations Subaponeurotic hemorrhage Subdural hemorrhage Skull fractures Retinal hemorrhage
Rotational forceps	Occipital osteodiasis Spinal injury

Image 12: A) Lungs from a term stillborn showing intraalveolar neutrophils and meconium (arrow) indicating congenital pneumonia and meconium aspiration (H&E, x100); **B)** smooth muscle pyknosis of the umbilical cord vessels (arrows) seen in intrauterine death (H&E, x400).

Equally, the presence of subdural hemorrhage or hemosiderin in any part of the dura should be interpreted with caution, since up to 46% of neonates may have asymptomatic subdural hemorrhage (51-53).

Retinal hemorrhages may also be related to birth, with a reported incidence up to 50%. These hemorrhages often involve multiple areas and layers of the retina and optic nerve (54), have been reported even in a small percentage of caesarean sections, and may last up to two months (55). As with subdural and intradural hemorrhages, a relationship with transient hypoxia is likely to exist in birth-related retinal hemorrhages without trauma. As the incidence of retinal hemorrhages following caesarean birth is much lower than following vaginal delivery, it has been suggested that raised intrathoracic and intracranial pressures related to the compression of the fetus in the vaginal canal are

not the only etiological factors (56). It has also been speculated that hypoxia and hypercapnia are contributory (56, 57). A study from Choi et al. reviewed the medical records of perinatally distressed newborns hospitalized at between 2006 and 2009 (57). The history of perinatal distress in this study included: birth asphyxia, meconium aspiration, placental insufficiency, transient tachypnea, pneumonia, and dysphagic choking. Under these conditions, the authors speculated that intraocular hemorrhages might result from significant hypoxic stress (57).

Congenital Infections

Intrauterine infections, acquired across the placenta through vascular dissemination or by ascending infection, are a common cause of stillbirth and early neonatal death (58-63). Acute chorioamnionitis with

Image 13: Bronchopulmonary dysplasia showing hyaline membranes (arrows) in a premature newborn (H&E, x200).

associated congenital pneumonia is the most common cause of congenital infection, usually caused by bacterial organisms (**Image 12A**). Placental examination, including histological sampling, must be part of the protocol. The infected fetus and placenta with chorioamnionitis may have an offensive smell. In infections by *Candida spp.*, small colonies develop on the surface of the cord and may be seen macroscopically as tiny white lesions (64, 65).

Histological examination of the placenta in cases of acute chorioamnionitis characteristically shows acute inflammation with neutrophilic infiltrate of the chori-

on (**Image 16**), amnion, and below the chorionic plate (subchorionitis). The inflammation then spreads up into the plate (chorionitis) and in the most severe cases causes necrosis of the amnion on the surface of the chorionic plate. The presence of plate vessel or cord vessel vasculitis (neutrophilic inflammation of the wall of the vessel from the luminal surface) indicates a fetal response to an ascending infection (64, 66). The most common causes of ascending infection are *Escherichia coli* and Group B Streptococcus (GBS). Group B Streptococcus may result in fetal death even with minimal chorioamnionitis. *Ureoplasma urealyticum* and *Mycoplasma spp.* are also frequently in-

Image 14: Lung histology in a perinatal asphyxia showing amniotic debris (stars) and pale-brown meconium pigment (arrow) (H&E, x200).

involved (42). Microbiology cultures and the pattern of involvement in the fetus may provide a clue to the diagnosis. Conjunctivitis and pneumonia would suggest *Chlamydia trachomatis* (67).

In cases of hematogenous infection to the placenta, the chorionic villi are usually the target of the infection. The inflammatory cells will range from neutrophils reacting to suppurative organisms to mononuclear cells reacting to the presence of a virus. TORCHS infections correspond to infections caused by *Toxoplas-*

ma gondii, rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), and syphilis. Villitis associated with CMV infection is characterized by the presence of plasma cells (**Images 17A to E**). The virus may infect the Hofbauer cells (villous stromal cells) or endothelial cells of the villous vessels. Viral inclusions are also seen in fetal epithelial structures (i.e., lungs, kidneys, and pancreas) as large rounded dense eosinophilic nuclear inclusion bodies. Even though these fetuses tend to be severely macerated, viral inclusions are easily identified. Herpes simplex virus is usual-

Image 15: Advanced thymic atrophy showing thinning of the cortex (linear bar) and early cystic changes in the Hassall's corpuscles (arrow) in a preterm neonate who succumbed to necrotizing enterocolitis (H&E, x100).

Image 16: Acute chorioamnionitis with focal necrosis of the amnion (arrow) due to *Listeria monocytogenes* (H&E, x200).

ly acquired during vaginal delivery in a mother with genital herpes, most often HSV type 2. The disease may be localized or diffuse, with the latter usually being fatal. Typical sites of involvement are the skin, mucous membranes, central nervous system, eyes, gastrointestinal tract, and adrenal glands (64). Characteristically, intranuclear inclusions are seen at the periphery of foci of coagulative necrosis.

Parvovirus may also cause stillbirth. This virus infects pronormoblasts, causing severe anemia and hydrops fetalis. The viral inclusion can be seen in the nuclei of fetal nucleated red blood cells (**Images 18A and B**) (68).

Microbiology and immunohistochemistry constitute a valuable resource for the identification of the specific etiological agent involved.

Image 17A: Trophozoite cyst in the placental membranes (arrow) in a case of congenital toxoplasmosis (H&E, x400)

Image 17: B) Cytomegalovirus with nuclear inclusions (arrow, Cowdry type A) with “owl eye” morphology in the heart (H&E, x400), and **C)** brain of a macerated fetus (H&E, x600).

Image 17: Herpes simplex virus type 1 congenital infection showing **D)** liver necrosis (arrow) (H&E, x100); and **E)** viral inclusions (arrow) (H&E, x600); and **F)** confirmed with immunohistochemistry (arrow) (anti HSV type 1, x600).

Image 18: Severely macerated fetus showing advanced maceration of all organs. **A)** Parvovirus intranuclear inclusions are seen in the liver (arrows) (H&E, x200) and **B)** confirmed with parvovirus immunohistochemistry (arrows show the nuclear positivity) (x200).

Listeriosis is a bacterial infection acquired by blood spread via the placenta. The placenta presents with microabscesses in the chorionic villi and acute chorioamnionitis. With fetal infection, multiple organs such as the skin, liver, adrenal glands, spleen, and lungs have microabscesses. Gram stain will demonstrate small intracellular coccobacilli (64).

In the last decade, there has been an increase in the number of cases of congenital syphilis and, more recently, Zika virus has also been implicated in stillbirths (69).

Congenital syphilis causes hydrops fetalis with a large, pale, edematous placenta. Histologically, Warthin-Starry stain shows numerous spirochetes both in fetal and in placental tissues.

Metabolic Disorders

Inherited metabolic diseases (IMD) are caused by inherited defects in the enzymes/proteins or cofactors that metabolize protein, carbohydrate, and fat. These disorders are the result of molecular mutations/deletions that alter metabolic pathways through deficient or absent activity of a protein (enzyme). Frequently, identified disease-associated gene variations are of the missense type with the potential to produce abnormal enzyme conformation due to misfolding (69, 70). The

most common types of IMD include defects of fatty acid oxidation and defects of ketogenesis (71).

At postmortem examination, the main gross features may include pale discoloration and enlargement of the liver and heart; cerebral edema (in hyperammonemia); pericardial, pleural, and peritoneal effusions; and left ventricular hypertrophy or dilatation. Subendocardial fibroelastosis has often been described in many of the long chain fatty acid oxidation defects (72-74) (**Image 19**).

Histological features that may suggest the presence of IMD include hepatic fibrosis (in urea cycle defects) and macro- and microvesicular steatosis in the liver, heart, and muscle (**Images 20A to C**). Deposition of fat in renal tubular epithelial cells is a more specific indicator of a possible fatty acid oxidation defect (**Image 20D**). The type of stain used to demonstrate the presence of fat is dependent on the preferences of the pathologist. Oil red O is perhaps more frequently used, necessitating that fresh frozen tissue is procured at the time of the postmortem examination (**Images 20C and D**). Osmium tetroxide is another lipid stain, although blackening by unsaturated lipid is too unpredictable to demonstrate lipid in tissues. (74). The amount and location of the fat droplets in fatty acid oxidation defects, however, varies greatly with occasionally patients showing relatively scanty fat deposi-

Image 19: Enlarged heart with pale endocardium due to subendocardial fibroelastosis, **A)** fresh and **B)** after formalin fixation.

tion (72). Carnitine pantoictransferase II deficiency and severe, multiple acyl-Coenzyme A dehydrogenase deficiency may present as cystic dysplasia of the kidneys (**Image 21**). Electron microscopy is a useful investigation in fatty oxidation and mitochondrial respiratory cell defects as mitochondria may show abnormal features such as enlargement, increased number, or a condensed appearance.

In carbohydrate disorders due to defects of fructose, galactose, and glycogen metabolism and storage, liver histology may show diffuse steatosis, pseudoacinar changes, focal hepatocellular necrosis, variable periportal and intralobular fibrosis, and ductular proliferation. The kidneys may show dilated tubules with swollen epithelial linings (72). In certain IMD, changes can be more specific: in glycogen storage (GSD)

disease type I (glucose-6-phosphatase deficiency or G6PD), the histology shows uniform distention of liver cells due to the accumulation of glycogen in a mosaic pattern. In GSD type II (Pompe disease), there is generalized glycogenosis with cardiomegaly, hepatomegaly, and macroglossia. In GSD type IV (amylopectinosis), diastase-resistant amylopectin is present in peri-portal hepatocytes with associated steatosis and variable progression to cirrhosis. The amylopectin deposits are also identified in the cardiac and skeletal muscle. Electron microscopy demonstrates the presence of abnormal glycogen accumulation (75).

Placental Causes of Stillbirth

It is fundamental to examine the placenta in all cases of stillbirth, and if available, in early neonatal death.

Image 20: Macro and microvesicular steatosis as seen in **A**) liver (H&E, x100) and **B**) heart (H&E, x200), and confirmed in **C**) liver (oil red O, x200) and **D**) renal tubules (arrows) (oil red O, x200).

Some placental conditions associated with IUD and IUGR may recur in future pregnancies. Appropriate placental sampling is essential. A minimum of a membrane roll, two sections of umbilical cord, and three sections of normal placenta should be taken, as well as representative sampling any lesions encountered (76).

The pathologist should be able to assess placental villous maturation since both accelerated and delayed maturation may be associated with IUD.

Maternal vascular malperfusion describes placental abnormalities consisting of accelerated villous maturation and lack of transformation of the maternal spiral arteries in maternal decidua together with the presence of trophoblast giant cells. The changes are frequently seen in maternal hypertension and especially in preeclampsia and may be associated with IUGR. Severe maternal vascular malperfusion with typical

villus changes plus infarcts is an important cause of IUD (76, 77). Delayed maturation, on the other hand, is frequently associated with maternal diabetes or a predisposition to diabetes and may be associated with late third trimester IUD (**Image 1A**) (59).

Placental abruption can be diagnosed by the pathologist if there is a retroplacental clot. If the mother had an acute abruption with marked blood loss but no clot, it is difficult for the pathologist to establish the diagnosis. However, stillborn babies due to placental abruption tend to be fresh with severe congestion and more numerous petechiae (78). If there is a retroplacental clot, indicating a degree of chronicity and a combination of hypoxia/acidosis and increased retrograde blood pressure in the head and thorax, it is frequent to see extensive but nonspace occupying subdural, intraventricular, and intraparenchymal hemorrhages (26, 43, 79).

Image 21: Early neonatal death due to carnitin pantoic transferase II deficiency showing dysplastic kidneys (H&E, x200).

Blunt trauma to the abdomen increases the risk of placental abruption and fetal outcomes correlate with the severity of the trauma (60). Stab wounds to the pregnant woman with severe blood loss may cause fetal death due to severe hypovolemia.

Two conditions of probably autoimmune origin are associated with IUGR and IUD in the third trimester: villitis of unknown etiology (VUE) and massive perivillous fibrin deposition (MPVFD) (76, 80, 81).

Villitis of unknown etiology is an inflammatory condition in which lymphocytes but no plasma cells infiltrate chorionic villi. The severity of the condition is variable (76). As opposed to chronic villitis associated to viral infections, VUE typically presents in the third trimester in small placentas.

Massive perivillous fibrin deposition (also known as maternal floor infarction) is a placental disorder with a very characteristic macroscopic placental appearance. The placentas are small and hard, and on cut section show a marbled appearance (82). The fibrin deposition should be distinguished from placental infarcts (**Image 22**). Both VUE and MPVFD may recur in future pregnancies and if diagnosed the mother's obstetrician should be informed.

Some umbilical cord problems can be diagnosed at autopsy. However, the pathologist rarely receives the whole umbilical cord and certain conditions, such as cord prolapse or intermittent cord compression, may not leave any apparent changes in the cord or the placenta. On the other hand, umbilical cord hematomas, knots, strictures, thrombi, or necrosis can be associat-

Image 22: Massive perivillous fibrin deposition characterised by fibrin occupying the intervillous space (arrows) (H&E, x100).

ed with adverse fetal outcomes if the resulting vascular compromise is significant (83).

CONCLUSION

This review presents the forensic pathologist with a quick guide on how to approach a perinatal postmortem, be it of a fetus found somewhere or a hospital medicolegal case. Forensic aspects of perinatal death may include estimation of the gestational age if fetal remains are found; determination of the cause and manner of death and if this was natural, unnatural, or undetermined, and identification of any underlying condition that could have contributed to intrauterine or neonatal death. Consideration should be given to consult a perinatal pathologist and a neuropathologist in difficult cases.

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