

THE ROLE OF PLACENTAL EXAMINATION IN THE DIAGNOSIS AND TREATMENT OF NEONATAL ILLNESS

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Despite significant improvements in obstetric care, the incidence of prematurity continues to increase at an alarming rate. According to the March of Dimes, approximately 13% of all infants in the US are considered premature, an increase of 1% in the past 10 years. Although advanced maternal age, increasing rates of maternal obesity, and the widespread use of assisted reproductive technologies significantly contribute to this phenomenon, a variety of other factors appear to be important. For example, marked inflammatory changes in the maternal and fetal membranes and vessels (chorioamnionitis, funisitis, vasculitis) are routinely documented on histologic examination, with bacterial or viral infection now believed to be intimately involved in the pathogenesis of PROM, preterm labor, and premature delivery. This is critically important since antenatal inflammation (cytokines) and infection has now been demonstrated in multiple studies to initiate a complex cascade that can ultimately result in the development of bronchopulmonary dysplasia, intraventricular hemorrhage, and periventricular leukomalacia (PVL). MRI examination at the time of preterm birth can demonstrate PVL, suggesting that the same process that causes preterm delivery may also cause PVL. Histologic examination of the placental is vital in order to establish the presence of inflammation and infection.

Despite marked increases in the rate of cesarean section delivery, the incidence of cerebral palsy (CP) has not significantly decreased in term infants. This reinforces the concept that intrapartum events do not extensively contribute to the incidence of CP. Once again, chorioamnionitis, funisitis, and vasculitis (with clot formation) may help explain why an infant is depressed at birth and in need of resuscitation. Infants developing unexplained respiratory failure, abnormalities on neurologic examination, and seizures would also benefit from histologic examination of the placenta in order to better understand the etiology of these events. If an infant develops seizures on day 2 of life and a cerebral infarct is diagnosed by CT or MRI, clinicians often forget to request that the placenta be sent to pathology for processing, especially if the infant was initially stable following birth. This is crucial since chorioamnionitis and vascular/pro-thrombotic phenomena may be responsible for the abnormalities.

Placentas should be retained in a refrigerator at least until the mother and child are discharged and ideally for 1 week (in case the child is readmitted). Placental examination should include a gross examination along with a description of the disk shape, surface, and thickness. The distance from the cord insertion to the nearest margin should be measured and any meconium staining should be noted. Membrane staining may develop within several hours, but cord staining is much less common and thus denotes a longer passage-delivery interval. For that reason, if the cord is green it should be specifically noted. Placental tissue sampling should include at least one and preferably two cross sections of the umbilical cord, one membrane roll (including membranes from their ruptured edge to the disk margin), at least 2 full thickness sections from the central placenta, and one section from each lesion that is identified on gross examination.

The role of histologic examination of the placenta in the clinical management of the mother and infant has been the subject of some controversy. This is partly due to a history of poor communication between pathologists and clinicians, as well as problems with significant interobserver variability among even “expert” pathologists. However placental examination is essential in any case in where: 1. significant maternal illness existed that could potentially influence present and future pregnancies (e.g. diabetes, pre-eclampsia), 2. *in utero* interventions have been used in order to assess success (e.g. heparin to prevent placental vascular thrombosis), 3. the fetus had abnormal fetal heart rate monitoring, ultrasound examination, or biophysical testing, 4. an infant is depressed at birth and needs intervention, 5. an infant has an abnormal physical examination and/or clinical presentation at birth, and 6. an infant is stable at birth, but subsequently is found to have significant respiratory distress, neurologic abnormalities, or another medical illness.

The use of anticoagulant therapy in obstetrics has increased dramatically over the last decade, but it remains problematic to determine which mothers who may have inherited or acquired thrombophilias actually **need** anticoagulant therapy to maintain their pregnancy. The use of placental pathologic evidence of injury due to maternal vascular thrombosis is recommended as both biologically appropriate and cost-effective. What is clear is that placental pathology diagnostics can be used to better understand future maternal health risks, as well as in any case in which a subsequent pregnancy is a possibility.

From the point of view of understanding the neonatal neurologic injury, placental examination is a comprehensive and cost-effective tool. While chorioamnionitis is recognized as a major predisposing factor for cerebral palsy, the overwhelming majority of cases are clinically silent either in terms of maternal or neonatal symptoms. The presence of chorioamnionitis and the fetal inflammatory response have been correlated with abnormal fetal heart rate patterns. In a unique data set, histologic evidence of funisitis has been shown to be associated with decreased scores on biophysical profiles within 24 hours of delivery. However, abnormalities in fetal heart rate monitoring, biophysical profiles, and umbilical arterial Doppler studies are unreliable **predictors** of intraamniotic infection.

The diagnosis of fetal hypoxia is also clinically problematic. While normal umbilical cord pH rules out significant fetal hypoxia occurring shortly before delivery, a low pH can occur with a variety of conditions such as placental insufficiency (e.g. abruption), infarction, or infection. A reduced estimated fetal weight or a change in fetal growth may reflect fetal compensation in response to reduced nutrient and possibly oxygen availability. Determination of placental weight centiles, the fetoplacental weight ratio, and the gross identification of placental infarcts, thromboses and abruption can identify the cause of an antenatally identified fetal abnormality, and mark those infants who may benefit from closer neonatal follow-up. Histologic markers of fetal hypoxia (villous fibrosis, abnormal capillary networks, syncytial knotting, increased perivillous fibrin) have also been shown to be unreliable. We have developed sets of image-segmentation algorithms that reliably isolate and quantify the villous features consistent with placental injury. These algorithms are currently being compared to a range of biologically appropriate parameters. Such biologically relevant endpoints will hopefully yield reliable and quantitative diagnoses of placental features with predictive value for clinically relevant endpoints, including abnormal neurodevelopmental outcome.

Although bacterial infection of the placenta, the presence of chorioamnionitis, and poor outcome in the newborn has been established, the role of viral infections has not been well delineated. Correlation of histologic features of the placenta with *in situ* detection of viral or bacterial nucleic acids in cases of severe morbidity and mortality in the neonatal period has been performed. Seventy-seven placental tissues were analyzed with a consensus bacterial probe and for a wide variety of viral infections. An infectious cause was found in 46/60 (76%) of cases from enterovirus, bacteria, cytomegalovirus, herpes simplex, and parvovirus. The infectious agents localized primarily to Hofbauer cells and trophoblasts. In each of the cases where autopsy material was available, the same infectious agent that was detected in the placenta was also detected in the autopsy material (spleen, heart, central nervous system, or lungs). No infectious agent was detected in any of the controls. Viral inclusions and stem vessel vasculitis were the only histologic findings that were associated with infections of the placenta. These data show that: 1. infection of the placenta is highly associated with neonatal morbidity and mortality; 2. histologic findings are mostly non-specific for infection; and 3. viral infection appears to occur more frequently than expected, with coxsackie virus infection particularly important in this process.

In summary, histologic examination of placenta is a crucial element in neonatal-perinatal care. The placenta should always be sent to Pathology when there is significant maternal or neonatal illness requiring medical intervention. Although the presence of chorioamnionitis and funisitis may be indicative of an underlying bacterial infection and can explain the development of significant respiratory or neurologic abnormalities, viral infections may also be responsible for severe neonatal morbidity and mortality. These can now be detected with advanced molecular techniques and should be considered in cases of unexplained and severe illness.