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Macroscopic and Histopathological Study of the Placenta - An Essential Resource in Litigation Processes

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Abstract

The pathological study of the placenta is of upmost importance in cases of unexplained fetal/perinatal loss and often these carry litigation implications. Integrating pathological findings and the underlying pathophysiological processes, leading to placental lesions, is fundamental for the evaluation of poor fetal and perinatal outcomes and to distinguish from cases of true negligence.

Keywords: Placenta; Litigation process; Pathology study; Histopathology

Overall Perspective

Understanding the placental function has been crucial for a clinical and well-founded interpretation of pathological alterations associated with poor obstetric outcomes. The anatomopathological study of the placenta allows the investigation of unforeseen cases of fetal/perinatal loss, while further developing our knowledge of some neonatal diseases. The significance of this study is even greater if one considers that about 3/1,000 children will suffer of some sort of cerebral palsy [1-4]. The increase of litigation processes towards hospitals and obstetricians is a reality and in most cases, the litigant part claims negligence. Setting aside, well documented cases of true negligence, one must consciously and responsibly select cases with pathology associated with a poor obstetric outcome. For this purpose, the study of the placental is fundamental [5]. It is important to note that, the aim of this article is not to describe any epidemiological study of specific cases of placental disorders but, to emphasize that the study of the placenta may reveal undiagnosed or unsuspected pathologies in cases of poor obstetric outcomes that explains and justifies fetal/perinatal loss.

Placental pathological features and adverse fetal outcome

Implantation anomalies can lead to velamentous cord insertion with or without vasa previa, to placental accrete and/or to placenta previa and it is well documented its relationship with neurological damage and increased risk of fetal loss [6,7].

Placental infarction is a pathological condition of unknown etiology with distinctive features and has been associated with fetal intrauterine growth retardation (IUGR), microcephaly and neurological complications [1,8].

Decidual arteriopathy is a type of injury diagnosed only histologically and usually occurs as result of maternal circulatory disorders, such as pre-eclampsia, hypertension, antiphospholipidic syndrome and thrombophilia. It is also associated with placental poor perfusion and low weight, leading to IUGR [6,9]. The period of time that, placental lesions take to evolve and extend, and how they become installed are determining factors for fetal complications. The most common example is the abrupt placenta, a serious condition in which, the time period taken to develop a retroplacental hematoma is crucial for the macroscopic interpretation of the lesion and is critical to understand fetal complications. When fetal death does not occur, neurological damage is usually frequent [2,3]. Similarly, placental infarctions have consequent fetal complications according to the time of occurrence, location, extension and its progression. Massive perivillous fibrin deposition is the main diagnostic features of maternal floor infarction, a placental lesion reported to be as high as 1 of 200 placentas. The cause is unknown but, congenital infection, immune-mediated rejection and abnormal extravillous trophoblastic proliferation have been suggested etiologies in part because of its recurrent nature.

Fetal vessel thrombosis is a type of lesion singularly diagnosed with histology and greatly related to prematurity and increased incidence on fetal thrombosis and neonatal neurological complications [4,8,10].

Infections are common and highly contagious situations, with infra-clinical rates in 10% to 15%. It may reach the placenta and fetus in several ways: by ascension from tract vaginal infections, by hematogenous transmission from maternal blood by direct introduction via amniocentesis, chorionic villus sampling and other invasive diagnostic procedure or by direct extensions from infection in the endometrium. It is well known an association with fetal loss and cerebral palsy [7]. Hematogenous infection can result in fetal loss due to anemia following *Parvovirus B19* infection or lead to severe fetal disease due to toxoplasmosis and/or cytomelovirus (CMV) infection [11,12]. Definitive diagnosis of an infectious disease can be established by histological observation of a characteristic inflammatory infiltrate

and of pathognomonic viral inclusions associated with CMV and parvovirus infection. When, morphological criteria are not fully present, the study should be completed with immunohistochemistry or other laboratory techniques, such as molecular analysis. The ascending/adjacent infection is a subclinical condition that is present in about 20% of cases. Of these, histology analysis allows the diagnosis of acute/subacute chorioamnionitis and should always be classified according to the stage, degree and as possible with dating time evolution by the presence of hemosiderin. Chronic chorioamnionitis is a medical condition with pathogenesis not yet determined and diagnosed only with histological examination. This condition has been demonstrated to be associated with maternal hypertension, diabetes, IUGR, oligohydramnios, hydrops fetalis and poor perinatal evolution [13,14].

Massive chronic intervillositis is a medical condition also singularly diagnosed with histology and is associated with IUGR and fetal death and commonly described in recurrent abortions. In 70% of cases, this condition is present simultaneously with chronic villitis and is related to prematurity and neurological injury [15]. Chronic villitis occurs in 5% to 10% of all placentas and higher percentage is well documented when placenta of complicated pregnancies are studied. At times infectious etiology is apparent however, in majority of cases no specific etiology is elicited and the term villitis of unknown etiology (VUE) is used. There are no doubts that VUE is a recurrent lesion with occurrence rates of 10% to 25%. Two theories are postulated with respect to the etiology of VUE. One suggest that is an infectious disease caused by a yet unrecognized agent and other suggest an immune reaction supported by the preferential localization of these lesion and type of inflammatory cells. VUE is also associated with prematurity, abnormal neurologic development and intra-uterine fetal demise [16].

The etiology of "ADAM complex" (amniotic deformities, adhesions and mutilations) is widely discussed as its incidence is difficult to document and studies suggest a rate of 1/2,500 to 1/10,000 newborns. Amnion rupture will cause, by mechanical way, amniotic bands or sheets, leading to fetal amputations, anomalies or even demise. The amnion rupture etiology is unknown however, it is important to note that this is usually nonrecurring but the fetal pathological condition is presented with a varied pattern related with the time of occurrence and can result in severe malformations if it occurs prematurely, mimicking trisomy 13 phenotype, or minor malformations sometimes not prenatally detected.

On the other hand, the color change in the placenta has a distinct pathogenesis. About 20% of newborns present a green placenta related to meconium and it is believed that fetal distress is due to vasoconstrictor effect, inducing vascular muscle cell necrosis and compromising the return of the venous oxygenated placental blood [17,18]. In premature newborns, the same color can translate in hemosiderin deposits associated with retromembranous hematoma, with risk of fetal-maternal transfusion, fetal hemolysis and thrombocytopenia [19]. In turn, the alteration in parenchyma color reflects the hemoglobin content of the villi and, when pale, usually translates in fetal hydrops/anemia, with heterogeneous etiology and regularly in neurological damage.

Villi morphology when histologically evaluated is correlated with gestational age and deviation from normal development is usually classified as: (i) maturation arrest/delay, reflecting maternal or fetal pathology and (ii) advanced maturity, reflecting poor perfusion and low weight with fetal/neonatal hypoxia and death[15,20]. When fetal death occurs, determining time of death *in utero* is always important and is based in macroscopic and histological changes of the placenta and fetus [21,22].

Chorangiosis is an alteration that results from an abnormal proliferation and capillary neovascularization process associated with prolonged fetal hypoxia and even though the significance and integration into the fetal-placental unit is not completely understood, recent studies have shown its correlation with perinatal complications [23].

Erythroblastosis usually correlates with hypoxia, infections, bleeding and hemolytic anemia and it can be associated with genetic or epigenetic disorders, being also described as a secondary effect of trauma [19,24].

Fetal injuries in cases of mesenchymal dysplasia are well reported and it is known that about 1-2% of this change, often unsuspected, is associated with placental mosaicism [25].

The intrinsic placental lesions correspond mostly to primary tumors, where chorangioma is the most frequent and have an increased risk of fetal morbidity/mortality. Gestational trophoblastic diseases are not true neoplasm. However, they are associated with an increased risk for the development of neoplasm, specifically choriocarcinoma. Other gestational trophoblastic disease like placental site nodule and exaggerated placental site, are not grossly identifiable, unlike placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT) are generally evident as infiltrative masses. Usually these situations do not pose any problem in litigation process. Chorangioma and gestational trophoblastic disease require an appropriate clinical follow-up due to the risk of recurrence and malignancy, or even more aggressive disease like can occurs in PSTT and ETT.

In twin pregnancies, in order to understand the origin of fetal lesions and repercussions, it is essential that the physician provides adequate a referencing of fetal umbilical cord. It is the pathologist's responsibility to document: (i) the relationship between membranes/division septum and their correlation with the chorionic/vascular equator, and chorionicity; (ii) the presence of vascular anastomosis (VA) with or without criteria for twin-to-twin transfusion syndrome (TTTS) and (iii) the relationship and insertion type of umbilical cords. Both cord's pathology and pathology related to the presence of VA are well documented and understood. Secondary vasculogenic organ damage and destructive lesions can occur in the survivor after fetal death of one twin, particularly in monochorionic twins, while polyhydramnios and oligohydramnios are most frequently found in chronic TTTS and yet justify the discrepancy of fetal growth [25].

What type of placentas should one select for the anatomopathological study?

Selecting a cohort of placentas to study it is not a consensual matter and may be based on specific clinical criteria, consist in macroscopic examination of all placentas and microscopic study of specific cases or be restricted to cases of fetal/perinatal complications with/without diagnosed or suspected maternal problems [26,27].

It is essential that the selection of placentas is accompanied by the complete clinical information for the diagnostic to be integrated and useful. The obstetrician should gather/provide all relevant clinical information and a list of issues to clarify; while the pathologist is responsible for studying the placenta to establish a diagnosis that

integrates pathological findings with clinical implications [27-30]. The pathological diagnosis should be integrated considering: (i) maternal age and invasive diagnostic and therapeutic procedures, including medically assisted reproduction techniques; (ii) gestational age and maturation-related deviations and (iii) traumatic injuries, including road traffic accidents, which many times present clinicopathological features similar to other conditions such as abrupt placenta, infarctions, hemorrhagic villitis and/or intra-amniotic hemorrhage [6,27,31].

Conclusion

The development of standard guidelines and multidisciplinary clinical consensus would allow the establishment of an accurate protocol and reproductive methodologies that would assist in estimating adequate criteria for subsequent actions. Table 1 reports some situations with clinical indication for the anatomopathological study of the placenta [32] (Table 1).

Maternal Diabetes	Fetal/Neonatal	Placenta, membranes and umbilical cords
Pregnancy-induced or chronic hypertension	Fetal or neonatal death	Infarctions, including infarction of the placental bed
Premature Rupture of Membranes	Twin pregnancy	Placental abruption
Preterm birth (<36 weeks)	Prematurity	Vasa previa
Post-term birth (>42 weeks)	Intrauterine growth retardation (IUGR)	Placenta previa
Poor obstetric history	Hydrops	Any abnormal appearance of the umbilical cord membranes or of the placenta
Unexplained fever or infection	Congenital anomalies	
Oligohydramnios	Fetal/neonatal erythroblastosis	
History of drug use	Not reassuring fetal status / transfer to neonatal care unit	
	Ominous heart rate	
	Meconium discharge	
	Low Apgar score (<5 at 1' and <7 at 5')	

Table 1: Indications for anatomopathological study of the placenta.

In litigation processes, the pathologist is frequently called upon and questioned to clarify specific pathological processes and their evolution. The progress of infectious, thrombotic/ischemic events and the establishment of fetal time of death are questions frequently requested. These issues are sometimes challenging to assess due to the coexistence of competing injuries, requiring a confident understanding of its pathogenesis and implications. A cautious pathologist should minimize possible errors, always integrating the complexity of processes, thus avoiding an unfounded opinion that may be disputed.

It is essential to establish a good communication conduct between obstetrician and pathologist for the production of a clinically integrated and consistent report.

Keypoints

The progress on the knowledge and understanding placenta's function and its associated pathophysiological processes has allowed the placenta to become a reflection of intrauterine life.

The placenta's anatomopathological study is fundamental for the integration and comprehension of poor obstetric outcomes and plays an important role in litigation processes.

A functionally and macroscopically normal placenta can coexist with an adverse intrauterine environment and be the cause of fetal loss.

The anatomopathological diagnosis of the placenta should integrate lesions and its progression with consequent clinical implications.

Conflicts of Interest

The authors declare no conflict of interest.

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