

Placental Pathology:

A Chronicle of Intrauterine Life

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I. Introduction

The placenta is the largest organ of the fetus, and although it remains outside of the fetal body it is responsible for nurturing the fetus throughout gestation. It is an anatomically, physiologically, and biochemically complex organ having two independent blood supplies and forming the interface between two (and in cases of multifetal pregnancies three or more!) genetically distinct individuals – mother and infant. In many respects, the placenta is a diary of the intrauterine life (and, unfortunately, in some cases death) of the fetus. When examined by an expert in placental pathology, it can reveal the nature, severity, timing, duration, etiology, and effects on the fetus of a wide variety of pathological intrauterine processes which can affect the fetus. When these data are correlated with clinical obstetrical and neonatal outcomes data and results of evaluation of uteroplacental and fetal growth and development, the scientific explanation for poor obstetrical and infant consequences can often be explained with a high degree of probability.

Unfortunately, the number of *bona fide* experts in placental pathology is very small due to a variety of factors. Placentas are typically submitted to the pathology departments in those hospitals providing obstetrical services, and in which the pathologists typically do not have special expertise in this area. It is well-known that placental diagnoses made by non-specialists are often suboptimal and typically incomplete (Schwartz, DA. Challenges in improvement of perinatal health in developing nations – Role of perinatal pathology. *Archives of Pathology & Laboratory Medicine*, 2013, 137(6):742-746). In one peer-reviewed study, 92.7% of placentas had diagnostic discrepancies, most frequently underdiagnoses (failure to report a pathological finding(s)), when re-evaluated by a placental pathology specialist (Sun C-C, *et al.* Discrepancy in pathologic diagnosis of placental lesions. *Archives of Pathology & Laboratory Medicine*, 2002, 126(6):706-709). Thus, in order to maximize the amount of medical information contained within the placenta, it is important that it be reviewed by an expert in placental pathology.

Placental pathology is a dynamic scientific field – it remains at the forefront of many important obstetrical, perinatal and pediatric issues such as the cause(s) of stillbirth and neonatal deaths, etiology of brain injury and neurodevelopmental abnormalities, exposure of the fetus to toxic substances, and the development of intrauterine anomalies of fetal growth and development (Schwartz DA. Chapter 14. The pathology of pregnancy. In: *Rubin's Pathology. Clinicopathologic Foundations of Medicine*. 7th edition. D.S. Strayer and E. Rubin, eds.; J.E. Saffitz, and A.L. Schiller, assoc. eds. Wolters Kluwer/Lippincott, Williams & Wilkins. Philadelphia. 2014. Pages 535-562). Placental research has been of critical importance in the understating of the effects of intrauterine infectious diseases on the developing fetus (Schwartz DA. The placenta in maternal-fetal viral transmission and the congenital Zika syndrome: Hofbauer cells, trophoblast and chorionic villi. *Springer Nature. Expert Commentaries on the Zika Virus*. Published online on September 13, 2016. Available from: <http://www.springernature.com/gp/group/zika-virus/the-placenta-and-zika/10694152>). These infections include chorioamnionitis and ascending infections, blood-borne-infection, villitis, and emerging infections, most recently the Zika virus (<http://www.prnewswire.com/news-releases/archives-of-pathology-laboratory-medicine-to-publish-first-peer-reviewed-special-journal-issue-devoted-to-the-zika-virus-300381980.html>). Some causative placental lesions can have a risk for recurrence that can help direct obstetrical care in future pregnancies; placental pathology can also result in findings which are of immediate relevance to the health of the mother and her infant. And even in some cases of maternal death, examination of the placenta can provide clues to the occurrence of obstetrical diseases, leading to the identification of cause(s) of the mother's

demise (Schwartz DA. The pathology of maternal death - the importance of accurate autopsy diagnosis for epidemiologic surveillance and prevention of maternal mortality in developing countries. In: *Maternal Mortality: Risk Factors, Anthropological Perspectives, Prevalence in Developing Countries and Preventive Strategies for Pregnancy-Related Death*. DA Schwartz, editor. Nova Science Publishers, Inc., New York. October, 2015. Pages 215-253).

II. Severe Fetal Vascular Lesions

The category of severe fetal vascular lesions includes four important pathological findings affecting the fetal vessels and chorionic circulation of the placenta. The occurrence any of these abnormalities is associated with poor obstetrical outcomes for the fetus and neonate.

A. Meconium-Induced Vascular Necrosis (MIVN)

An important potential complication of intrauterine meconium discharge. In this condition, meconium passage by the fetus remote from delivery has sufficient time to penetrate the connective tissue (Wharton's jelly) of the umbilical cord, and/or through the chorionic connective tissue of the chorionic plate, thereby reaching and penetrating the muscular walls of the umbilical cord or large chorionic plate blood vessels. Once the meconium reaches the smooth muscle of the blood vessels, a toxic reaction occurs which results in apoptotic degeneration and necrosis of the smooth muscle cells over a period of several days or greater. Once blood vessels undergo smooth muscle necrosis due to MIVN, their function in regulating fetal blood flow becomes compromised. Because MIVN involves destruction of the walls of the major fetal blood vessels of the placenta, poor obstetrical outcomes are associated with its occurrence. These include perinatal death and neurological damage to the fetus, including cerebral palsy.

B. Chronic Villitis with Obliterative Vasculopathy

Villitis is the term used to signify an abnormal inflammation of the chorionic villi of the placenta. The villitides can result from maternal hematogenous infections with known microbial agents such as *Toxoplasma*, cytomegalovirus, syphilis and *Listeria* infections. Villitis of unknown etiology (VUE) results in an abnormal inflammatory process of the chorionic villi in which no infectious agent is found. VUE probably has multiple potential different etiologies, including as yet unidentified infectious agents. In severe cases of VUE, the villitis can be chronic, diffuse, and even necrotizing. It may involve the large, medium and terminal branches of the chorionic villous tree, resulting in villous necrosis, and/or destruction of chorionic villus blood vessels, termed obliterative vasculopathy. In these cases, chronic uteroplacental malperfusion and insufficiency can ensue. VUE can also recur in subsequent pregnancies, and pregnancy failures occur in about 60% of pregnancies complicated by recurrent VUE. Severe forms of VUE are associated with stillbirth, neonatal death, and intrauterine growth restriction (IUGR). Infants who survive may have neurological deficits including cerebral palsy.

C. Fetal Thrombotic Vasculopathy

Thrombosis occurring anywhere in the circulation of the placenta – termed fetal thrombotic vasculopathy or FTV – is always an abnormal finding, and indicates a deleterious intrauterine environment for the fetus. They can develop in either the arterial or venous circulation of the placenta and umbilical cord. Risk factors for development of fetal thrombotic vasculopathy include villitis and disorders of coagulation, particularly hypercoagulable syndromes. In some cases, there is no identifiable maternal risk factor for thrombosis. Clots forming in the placental circulation can have fearsome complications for the fetus, as they cause placen-

tal insufficiency by obstructing blood flow and thus perfusion in part of the villous trees. In chronic FTV, chorionic villi downstream from thrombosed vessels undergo progressive fibrosis, giving a distinctive appearance to clusters of scarred villi, and are termed avascular villi (AV). If larger chorionic vessels are thrombosed, over time the thrombus can attach to, and later be incorporated into, the vessel wall forming a mural thrombus, or cushion defect. A variety of poor outcomes are associated with FTV including stillbirth, neonatal death, intrauterine growth restriction and, in surviving infants, neurologic injury including cerebral palsy. Blood clots in the fetal placental circulation may occur together with blood clots in the fetal body, including lungs, brain and kidneys. Fetal thrombotic vasculopathy is often seen together with hemorrhagic endovasculopathy (HEV) and villitis of unknown etiology (VUE).

D. Chorioamnionitis with Severe Fetal Vasculitis

Acute chorioamnionitis is the microscopic hallmark of an ascending infection, almost always bacterial in origin. It can be associated with poor fetal outcomes including preterm delivery and premature rupture of membranes, perinatal death, sepsis, necrotizing enterocolitis (NEC), and neurodevelopmental injury. These outcomes are especially common in preterm, low (LBW), very low (VLBW), and extremely low (ELBW) birth-weight infants. Pathological chorioamnionitis consists of a maternal inflammatory response, or MIR, in which inflammatory cells derived from the mother infiltrate into the placental membranes (amnion and chorion). A fetal inflammatory response, termed an FIR, can be present in some cases. A FIR consists of fetal-derived inflammatory cells which migrate from the umbilical or chorionic circulation, resulting in vasculitis of the umbilical vessels (termed funisitis) and/or the large-sized surface vessels (termed chorionic plate vessels) of the fetal surface of the placenta and referred to as chorionic vasculitis). Severe fetal vasculitis is a severe fetal vascular lesion and is associated with cerebral palsy.

III. Placental Lesions Characterized by Increased Fibrin

Fibrin is a clotting protein that is normally present in the maternal circulation as it travels through the intervillous space of the placenta. Small amounts of fibrin become deposited in the placenta under normal conditions in three locations. Fibrin occurs normally under the fetal surface (chorionic plate) of the placenta where it is termed subchorionic fibrin or Langhan's stria, and results from eddying of maternal blood and, potentially, from fetal movement. Fibrin also deposits in small amounts adjacent to chorionic villi, termed perivillous fibrin. Fibrin is a normal and necessary component of the basal plate of the placenta, and is termed Rohr's fibrin where it faces the intervillous plate, and Nitabuch's fibrin in the deep part of the basal plate. A deficiency of Nitabuch's fibrin is the cause of abnormal placental implantation and adherence (placenta accreta, increta and percreta).

A. Increased Perivillous Fibrin

In some cases there is a pathologically increased quantity of fibrin which deposits in intervillous spaces and around chorionic villi. This fibrin can interfere with perfusion of the villi (and hence impair oxygen delivery to the fetus) by blocking oxygen-bearing maternal blood flow through the intervillous space. As intervillous fibrin deposits, fibrin in the maternal circulation accrues onto and around villi, blocks oxygen diffusion across villous surfaces and eventually causes ischemic necrosis of the villi. Increased perivillous fibrin may lead to poor obstetric outcomes, including intrauterine growth restriction (IUGR), neurologic injury and cerebral palsy. Importantly, when it accompanies other placental abnormalities, it can increase the risk of a poor obstetrical outcome in an exponential (synergistic) manner.

B. Massive Perivillous Fibrin Deposition

A severe and chronic condition resulting from markedly increased placental fibrin deposition is termed massive perivillous fibrin deposition (MPFD or MFD). The exact cause(s) of MPFD are unknown. In this condition, large amounts of fibrin deposit confluent in a transmural pattern, extending from the basal (decidual) part of the placenta up to the fetal (chorionic) surface. The dense fibrin fills the intervillous space and surrounds the villi, which over time results in villous ischemia and necrosis. MPFD can frequently result in poor pregnancy outcomes, including intrauterine growth restriction (IUGR), perinatal death, and in infants who survive, neurological injury.

C. Maternal Floor Infarction

A maternal floor infarct (MFI) is not a true infarct, but has some morphological features in common with MPFD. Unlike MPFD where the fibrin is transmural from maternal to fetal surfaces, in maternal floor infarction the excessive fibrin extends confluent across the width of the placenta, involving primarily the basal surface and decidua and extending upwards to involve the villi. The floor of the placenta is firm or rubbery, thickened and often discolored tan-yellow. Similar to MPFD, the villi which are involved with MFI are embedded in dense fibrin and are necrotic. MFI has the same perinatal outcomes as does MPFD. Up to 30% of women having had an MFI in the placenta of their infant will have it recur in a subsequent pregnancy.

IV. Toxic Exposures During Pregnancy

The most prevalent preventable toxic exposure to the fetus in the United States is from cigarette smoking. Cigarette smoking is the leading avoidable cause of morbidity and mortality in pregnant women and their infants. About 13% of women report smoking during the last 3 weeks of pregnancy, even more among pregnant adolescents (27% to 37%). Cigarette smoking during pregnancy is associated with a variety of poor obstetric and infant outcomes. However, cessation of maternal smoking when pregnancy is diagnosed in the first trimester virtually eliminates the majority of the excess morbidity and mortality. Carbon monoxide in cigarette smoke binds hemoglobin better than does oxygen. Resulting carboxyhemoglobin cannot carry oxygen, and so decreases oxygen delivery to the fetus and causes fetal hypoxia. In heavy smokers, fetal oxygen-carrying capacity may be reduced by up to 25%.

Cigarette smokers have an increased risk of pregnancy loss early in gestation (spontaneous abortion). Increased risk for spontaneous abortion is also elevated from maternal exposure to second-hand smoke – smoking of greater than 20 cigarettes per day by a house-mate increases the risk of early pregnancy loss by 81%.

Many of the obstetric complications of cigarette smoking result from vasoconstriction. In particular, nicotine in smoke is a potent vasoconstrictor. It reduces uterine and placental blood flow. It has cardiac and central nervous system effects, can readily cross the placenta and reaches higher levels in the fetal tissues and amniotic fluid than in the mother. Vasoconstriction occurs in the blood vessels of all anatomic components of the uteroplacental unit, including the uterine spiral arteries perfusing the placenta with maternal blood, the placental villous vessels absorbing and transporting oxygen and nutrients, and the umbilical vessels carrying placental blood to and from the fetus. Placentas of women who smoke can show a variety of findings of chronic uteroplacental malperfusion (chronic maternal underperfusion), including the small, atrophic and fibrotic chorionic villi of villous hypoplasia, Tenney-Parker change, villous agglutination, placental infarcts, increased fibrin and chorangiomas. Maternal cigarette smoking is the most important preventable cause of asymmetric IUGR.

Unfortunately, maternal cessation of cigarette or cigar smoking early in gestation does not mean that the fetus is safe from the ill-effects of tobacco use if there is exposure of the pregnant mother to second-hand smoke. Second-hand smoke exposure to the mother and fetus includes the combination of smoke entering the air from an ignited cigarette and smoke exhaled into the air originating from other smoker(s). Secondhand smoke is a Class A carcinogen, and contains greater than 7,000 chemicals, of which hundreds are toxic, and approximately 70 can cause cancer. Smoke that burns off the tip of an ignited cigarette or cigar and enters into the environment, and contains twice as much nicotine and tar per unit volume, 3-times as much carcinogenic benzo(a)pyrene, 5-times as much carbon monoxide, and 50-times the ammonia as does smoke that is inhaled. Second-hand smoke exposure during pregnancy has increasingly been linked to an increased risk of multiple adverse health effects to the fetus as well as the infant and child. These include attention-deficit hyperactivity disorder (ADHD), sudden infant death syndrome (SIDS), low birth weight (LBW), decreased lung function, increased frequency of respiratory and ear infections, and severe asthma. Genetic damage to the infant's DNA resulting from second-hand smoke can be equally as severe as that caused by maternal smoking.

V. Placental Indicators of Adaptation to Fetal Hypoxia

A. Chorangiogenesis

Normal terminal chorionic villi contain five to six or fewer fetal blood vessels. In chorangiogenesis, the terminal chorionic villi display a marked increase in the number of vessels resulting from capillary (endothelial) proliferation due to chronic fetal hypoxia. This villous endothelial proliferation is seen as an attempt by the fetus and its' placenta to increase the capillary surface area of the villous vascular network to acquire more oxygen in the face of chronic intrauterine hypoxia. The extent of vascular proliferation displayed in chorangiogenesis takes many weeks to develop. Although chorangiogenesis does not cause fetal damage, it is a microscopic marker of significant chronic uteroplacental insufficiency and fetal hypoxia due to other etiologies, and is a marker for a deleterious intrauterine environment (Schwartz DA. Chorangiogenesis and its precursors: underdiagnosed placental indicators of chronic fetal hypoxia. *Obstetrical and Gynecological Survey* 56(9):523-525, 2001). It can accompany placentas with chronic umbilical cord abnormalities, maternal anemia, diabetes, and a variety of placental findings of chronic malperfusion including villous hypoplasia, fetal thrombotic vasculopathy, increased fibrin, multiple infarcts, effects of maternal cigarette smoking, and villitis. Chorangiogenesis is correlated with perinatal circumstances that suggest long-standing hypoxia, and thus is seen more often in the placentas of infants admitted to neonatal intensive care units, and children with cerebral palsy. When chronic fetal hypoxia has been occurring for a lesser duration of time, earlier stages of chorangiogenesis can be present in which the villi are abnormally hypervascular, but not to the extent present in full-blown chorangiogenesis (incipient chorangiogenesis).

B. Nucleated Fetal Red Blood Cells (nRBCs)

Nucleated fetal red blood cells (nRBCs) can be present in placentas of fetuses with recent, subacute and remote fetal hypoxia. They are generally considered to be an adaptive mechanism of the fetus to hypoxia.

VI. Growth Abnormalities of the Placenta

To provide sufficient oxygen and nutrients to the developing fetus, the placenta increases in weight and size as gestation progresses. For example, for a singleton fetus the mean placental weight at 30 weeks' gestation is 316 grams, at 35 weeks it is 434 grams and at term (40 weeks) it averages 537 grams. An abnormally

small placenta ($\leq 10^{\text{th}}$ percentile for gestational age) can contribute to or cause a poor clinical outcome for the fetus, including neurological abnormalities and perinatal death. Abnormally large placentas ($\geq 90^{\text{th}}$ percentile) may also occur, and can result from villous edema, fetal hydrops, placental hemorrhage, syphilis, placental tumors and maternal diabetes. The relationship between placental and fetal weights is also important. This relationship, called the fetal–placental weight ratio (FPWR), is important to understand how chronic uteroplacental malperfusion, or placental insufficiency, can develop. At 40 weeks’ gestation, the average FPWR is 7.1. In other words, in the absence of co-morbid maternal, placental, or fetal disease, one gram of placental tissue can provide optimal oxygenation for up to 7.1 grams of fetal tissue. If the fetus is too large for its placenta, or the placenta is too small, an increased fetal–placental weight ratio can occur which contributes to a poor obstetric outcome. Unfortunately, this statistic is not evaluated in most hospitals. Abnormally thin placentas (<2 cm thickness at term) can also be associated with poor obstetric outcomes.

VII. Growth Abnormalities of the Fetus

There are two major types of intrauterine growth restriction (IUGR) – symmetric and asymmetric. Asymmetric IUGR is the most frequent form of growth restriction in developed countries. Also termed “head-sparing IUGR,” it develops when the placenta cannot provide adequate oxygen and nutrition to the fetus for a long period of time. Fetal soft tissues of the extremities (skeletal muscle mass) and body (subcutaneous fat, especially at the abdomen) undergo gradual wasting. The liver may also become smaller because of decreases in hepatic fat and glycogen stores. The infant with asymmetrical IUGR often has a normal body weight for gestational age and gender, and usually has a normal body length and head circumference. Because the head usually continues to grow while there is soft-tissue wasting, this is often termed “head-sparing IUGR.” Asymmetrical IUGR is generally believed to be an attempt of the fetus to compensate for chronic uteroplacental insufficiency by shunting available oxygen and nutrients to the head (brain) and chest (heart) at the expense of its soft tissues; it is *prima facie* evidence of chronic intrauterine fetal damage. It is diagnosed at the time of delivery by calculating a statistic termed the Ponderal Index; unfortunately, this value is not typically calculated by the medical care team, and thus many cases of asymmetrical IUGR go undiagnosed. In rare cases, asymmetric IUGR can become a mixed pattern of IUGR, occurring together with elements of symmetrical IUGR, if the uteroplacental insufficiency lasts long enough or is sufficiently severe. The resulting newborn with IUGR has a 5 to 10 times increased risk for perinatal mortality and morbidity as compared with a neonate who is not growth restricted. IUGR is also associated with neonatal hypoglycemia, meconium aspiration, persistent fetal circulation and neurologic injury.

VIII. Effects of Multiple Placental Pathology Abnormalities

It sometimes occurs in a pregnancy that two or more abnormal conditions or diseases occur in the mother, placenta, fetus, or all three. Multiple abnormalities occurring in the same pregnancy are referred to co-morbid conditions. During pregnancy, the co-morbid conditions may be of differing etiologies, severity, timing and duration, and may be, but are not necessarily, causally associated with one another. The occurrence of multiple placental pathology abnormalities occurring in the same placenta can have potentially ominous implications for the fetus. Multiple placental pathology abnormalities have a synergistic or exponential (multiplicative) effect on the fetus and its outcome, including neurological abnormalities such as cerebral palsy as well as perinatal mortality. In some cases, one lesion decreases the threshold for the next lesion to cause damage, which can then exacerbate the effects of subsequent abnormalities. This synergistic relationship is especially relevant when the lesions are of differing durations – an example would include a fetus with

chronic abnormalities of preeclampsia in its placenta (villous hypoplasia, placental infarcts and decidual vasculopathy) which then develops an acute abruption during labor.

IX. Conclusions

In cases of poor fetal and neonatal outcomes, as well as in cases of maternal morbidity and death, examination of the placenta by an expert can disclose valuable information which can disclose the underlying cause(s) of morbidity and mortality. As the placenta is a diary of intrauterine life, the correlation of the gross and microscopic findings in the placenta, together with a comprehensive evaluation of the uteroplacental and fetal growth and development, analysis of maternal medical conditions and risk factors, and review of published clinical outcomes data for the pathologic findings, is a sensitive and specific method for the objective medical evidence-based determination of the causes of poor pregnancy outcomes.

Abnormal Placentation: blighted ovum ectopic pregnancy placenta accreta, increta and percreta placenta previa. Nonneoplastic placental conditions and abnormalities. Infectious: acute villitis and intervillitis acute chorionic vasculitis & chorioamnionitis necrotizing funisitis specific infectious organisms umbilical vasculitis and funisitis. Placental Pathology in COVID-19. *Am J Clin Pathol.* 2020 Jun 8;154(1):23-32. doi: 10.1093/ajcp/aqaa089. Placentas were examined and compared to historical controls and women with placental evaluation for a history of melanoma. Results: Sixteen placentas from patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were examined (15 with live birth in the third trimester, 1 delivered in the second trimester after intrauterine fetal demise). Placental pathology involves insults in either the maternal or fetal vascular compartments or to the placenta itself. From: *Reproductive and Developmental Toxicology (Second Edition)*, 2017. Related terms: Drucilla J. Roberts, in *Reproductive and Developmental Toxicology*, 2011. This overview of placental pathology is ordered by compartment – maternal, fetal and placental. Placental implantation abnormalities. The placenta is a materno-fetal organ which begins developing at implantation of the blastocyst and is delivered with the fetus at birth. As the fetus relies on the placenta for not only nutrition, but many other developmentally essential functions, the correct development of the placenta is important to correct embryonic and fetal development.