



Placenta and Umbilical Cord Abnormalities Seen With Stillbirth

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Abstract: Placental lesions identified in cases of stillbirth are of clinical interest and are frequently invoked as having a causal role. However, most of the placental changes found in stillbirth are also seen in liveborn pregnancies, and are of uncertain pathogenetic significance. Much of the literature addressing placental lesions found in stillbirth is descriptive, listing cases of interest without adequate controls. Further, lesions are described qualitatively, often with inadequate description of examination and sampling protocols. In this manuscript we describe the placental characteristics that are most frequently listed in stillbirth case series, including entities associated with maternal diseases. First, we describe how macroscopic placental, cord, and membrane findings can provide answers to midwives and physicians at the time of delivery and how the placenta should be handled in the delivery room to optimize the histopathological examination. Second, we provide a brief organization of histological findings of the pathogenesis of conditions associated with fetal death.

Key words: stillbirth, placenta, pathology

Triage and Preparation of Placenta Specimens

Every hospital with an obstetrical service should compile a list of maternal and fetal conditions and events that require placental examination by its pathology laboratory (Tables 1,2). In particular, placentas from all stillbirths should be sent to the pathology department for examination.

Generally, a copy of the patient's prenatal and hospital admission record is provided to the pathologist. In addition, minimum information should be attached to the specimen, including maternal identifier information, pertinent maternal medical, surgical and obstetric history, the estimated time/date of fetal death, the time/date of birth, the weight, gestational age, and any obvious physical abnormalities of the fetus.

The placental pathologies associated with stillbirth can be divided into 5 groups. These include 2 groups that can be initially explored in the obstetrical suite: (1) macroscopic lesions of the placental disc, umbilical

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TABLE 1. Placenta and Umbilical Cord Lesions Associated With Stillbirth

Group I—lesions of the umbilical cord and placental membranes	
Insertion abnormalities	Velamentous insertion and membranous vessels, marginal insertion (Battledore), furcate insertion
Obstructive lesions	True knots, torsions, strictures, vasa previa, and umbilical cord prolapse
Disruptions by abnormal membranes	Early amnion rupture sequence (amniotic band syndrome)
Length abnormalities	Long cord; short cord
Coiling abnormalities	Increased coiling; decreased coiling
Group II—abnormal development of the villous parenchyma	
Shape abnormalities	Multilobation, accessory lobe(s), placenta membranacea
Implantation site abnormalities	Placenta previa, placenta accreta, increta, and percreta
Abnormal development of villous parenchyma	Abnormal persistence of branching and nonbranching angiogenesis, terminal villous hypoplasia
Group III—infectious processes	
Maternal inflammatory response	Chorioamnionitis
Fetal inflammatory response	Vasculitis of the fetal blood vessels of the umbilical cord and chorionic plate, funisitis
Infectious placentitis	Acute placentitis due to infectious agents,
Placental inflammation of unknown etiology	Chronic villitis of undetermined etiology
	Chronic histiocytic intervillitis
Group IV—compromise of the maternal circulation and/or fetal circulation and hematological disturbances	
Maternal circulatory lesions	Decidual vasculopathy
	Villous (parenchymal) infarcts
	Intraplacental (intervillous) thrombi
	Massive subchorionic hematoma (Breus' mole)
	Abruptio placenta (retroplacental hematoma)
Parenchymal fibrin deposition	Massive perivillous (intervillous) fibrin deposition (gitterinfarct)
	Maternal floor fibrin deposition (maternal floor infarction)
Compromised/abnormal fetal circulation	Thrombosis of fetal vasculature
Compromise of fetal and maternal circulations	Placental and/or fetal hydrops
Group V—Complications of monochorionic placentation	
	Cord accidents in monoamnionic-monochorionic gestation
	Twin-twin-transfusion syndrome
	TRAP sequence (twin reversed arterial perfusion)

cord, and placental membranes and (2) complications of multifetal placentation. The 3 other groups (3) abnormal development of the villous parenchyma, (4) infections, and (5) compromise of maternal and/or fetal circulation and hematological disturbances, depend on histological examination and other laboratory procedures.

After macroscopic inspection of the placenta in the obstetrical suite, the placenta should be placed in a 1 to 2 L container with 100 to 200 mL of normal saline. Large adherent clots and separated segments of umbilical cord should be placed

in the same container. The container should be labeled with the patient's name, date of maternal birth, and the time/date of the stillbirth. The label accuracy should be confirmed. The specimen may be stored in its container overnight at 4°C, if the pathology department is not accessible.

Examination of the Placenta, Cord, and Membranes in the Delivery Suite

Before transfer of the placental specimen, however, information valuable to physician

TABLE 2. Maternal, Fetal, Neonatal and Placental Indications for Placental Examination From Women and Infants Hospital of Rhode Island

Maternal indications
Systemic disorders with clinical concerns for mother or infant [eg, severe diabetes, impaired glucose metabolism, hypertensive disorders, collagen disease, seizures, severe anemia (<9 g)]
Premature delivery \leq 34 wk gestation
Peripartum fever and/or infection
Unexplained third-trimester bleeding or excessive bleeding > 500 cm ³
Clinical concern for infection during this pregnancy (eg, human immunodeficiency virus, syphilis, cytomegalovirus, primary herpes, toxoplasma, rubella)
Severe oligohydramnios
Unexplained or recurrent pregnancy complications (eg, intrauterine growth restriction, stillbirth, spontaneous abortion, premature birth)
Invasive procedures with suspected placental injury
Abruptio placentae
Nonelective pregnancy termination
Thick and/or viscid meconium
Premature delivery from > 34-37 wk gestation, severe unexplained polyhydramnios, history of substance abuse
Gestational age \geq 42 wk, severe maternal trauma, prolonged (> 24 h) rupture of membranes
Fetal/neonatal indications
Admission or transfer to other than a level I nursery
Stillbirth or perinatal death
Compromised clinical condition defined as any of the following: cord blood pH, < 7.0; Apgar score, \leq 6 at 5 min; ventilatory assistance, > 10 min; or severe anemia, hematocrit < 35%
Hydrops fetalis
Birth weight < 10th percentile
Seizures
Infection or sepsis
Major congenital abnormalities, dysmorphic phenotype, or abnormal karyotype
Discordant twin growth > 20% weight difference
Multiple gestation with same-gender infants and fused placentas
Birthweight > 95th percentile, asymmetric growth, multiple gestation without other indication, vanishing twin beyond the first trimester
Placental indications
Physical abnormality (eg, infarct, mass, vascular thrombosis, retroplacental hematoma, amnion nodosum, abnormal coloration or opacification, malodor)
Small or large placental size or weight for gestational age
Umbilical cord lesions (eg, thrombosis, torsion, true knot, single artery, abnormal coiling)
Total umbilical cord length < 32 cm at term,
Abnormalities of placental shape
Long umbilical cord (> 100 cm)
Marginal or velamentous cord insertion

and patient can be obtained by simple observation. We have found that after some period of rest, while in the delivery suite, patients are often very receptive to discussion based on fetal and placental findings. Though emotionally vulnerable, most patients are responsive to the offer of explaining pertinent fetal and placental findings that may be evident to care providers. After the experience of stillbirth, patients frequently express gratification

that they felt included in discussions and were able to begin to find closure in this way.

The Placental Disc

After immediate obstetrical care is completed, the patient's nurse or physician should inspect the placenta. This inspection should be performed keeping in mind not to disturb the integrity of the

specimen. The maternal surface should be examined for evidence of missing cotyledons suggesting retained fragments, particularly common in early gestational age stillbirths. Blood clots, adherent to the maternal surface may be fresh or partly organized and indenting the placental surface, findings that are indicative of placental abruption.

The fetal surface of the placental disc should be inspected for color, light reflex, and adherent masses. It may appear stained with meconium. If, after gentle wiping of the amnion, green staining of the membranes persists, this suggests fetal meconium passage over 12 hours before birth. In cases of amnionitis, a dull light reflex and adherent purulent material may characterize the amnion. Cases in which marked oligohydramnios may have preceded stillbirth, amnion nodosa (adherent 1 to 2 mm white small nodules) may be found affecting the amnion.

Placental infarcts are commonly observed in the placentas of normal live fetuses, but these are usually found at the periphery of the placenta and are limited in number and size. In stillbirths, placental infarctions may occupy the central portion of the placenta. The infarcts tend to be larger and may extend the full thickness of the placenta with a lobular configuration and a distinct border. When more than 50% of the residual placental mass is infarcted most perinatal pathologists will identify infarction as a cause of mortality.^{1,2} As the infarct ages, it changes from dark red, when it is fresh, through brown-yellow-orange to white in temporally remote lesions.

The Umbilical Cord

Developmental abnormalities and accidental lesions of the umbilical cord and fetal blood vessels are the main causes of compromise of fetal macrocirculation.^{3,4} The umbilical cord should also be inspected for abnormalities in insertion, length, coiling, and focal lesions. The umbilical cord

may show signs of attenuation of Wharton's substance, rupture, hemorrhage, thrombosis, looping, and knotting.

VELAMENTOUS INSERTION

Velamentous umbilical cord insertion describes entry of the umbilical vessels into the fetal membranes rather than onto the placental disc. Velamentous cord insertion is found in 0.5% to 1.5% of all placentas,⁵ 1% of singleton, and up to 9% of twin pregnancies. It is found in approximately 1% of stillbirths, generally in multifetal pregnancies.

Velamentous cord insertion may suggest poor placentation with decreased chorionic and placental vascularization. This may explain the reported association between velamentous cord insertion and low birth weight and congenital anomalies. At the membrane insertion site, the umbilical cord is unsupported by the placental disc and is thus subject to kinking of the cord and vessel obstruction. At this point, umbilical vessels usually branch in the fetal membranes without the protection of Wharton's substance and unsupported by villous tissue.

Most velamentous cords insert relatively close to the placental disc. The distance between cord insertion and the disc margin and the length of the membranous vessels, provide a measure of the degree of their vulnerability. Membranous vessels are not limited to cords with velamentous insertion but may arise aberrantly from marginally or even centrally inserted cords, and may supply accessory lobes.

Membranous vessels proximate to the cervix are vulnerable to traumatic rupture and hemorrhage with fetal exsanguination during labor. Such ruptures are associated with perinatal mortality rates as high as 60% to 70%. In addition, compression and thrombosis of the umbilical cord may occur in this condition, especially when membranous vessels lie between fetus and internal cervical opening.

Thrombosis may occur in membranous arteries and veins, producing fetal thromboembolism and fetal death.

MARGINAL (BATTLEDORE) INSERTION

Marginal cord insertion describes umbilical cord insertion at the edge of the placental disc. This occurs in about 7% of placentas.³ Peripheral cord insertion (velamentous, marginal, and markedly eccentric) has been associated with discordant growth and growth impairment in twins. The major risk of peripheral cord insertion is rupture of the fetal blood vessels at the time of membrane rupture or during the second stage of labor (ruptured vasa previa).³ Twisting of umbilical vessels at the peripheral insertion site can lead to progressive variable decelerations and fetal acidosis. In extreme cases, vascular rupture or occlusion by thrombosis may be observed.

FURCATE INSERTION

In furcate insertion, the cord loses its Wharton's substance before insertion, leaving the umbilical vessels exposed. Furcate cords may insert velamentously or into the placental disc. The unsupported vessels are subject to compression, trauma, rupture, and thrombosis.

TRUE KNOTS

True knots are found in 0.5% of cords, but are more common among male fetuses, monoamniotic twins, multiparous women, and gestations complicated by hydramnios, fetal growth restriction, or long umbilical cords.³ They are associated with an overall perinatal mortality rate of 8% to 11%.⁶ When true knots are associated with visible venous distension in the distal (placental side) to the knot, persisting cord compression after the knot is reduced or presence of mural thrombosis especially in the vein, they are considered clinically significant. Umbilical knots should be left undisturbed to allow for

appropriate pathological inspection in the laboratory.

FALSE KNOTS

False knots are not actual knots. They are focal ectatic enlargement or varicosity of umbilical vessels. False knots are generally of no clinical significance and only rarely cause thrombosis.

UMBILICAL CORD TORSION

Cord torsion is the pathological accentuation of the normal helicoidal twisting of the cord, most often localized at the fetal end, and is associated with multigravida and male fetuses. Antemortem examples may show congestion, edema, and thrombi.^{7,8} Torsion may be 1 cause of nonimmune fetal hydrops because of intermittent cord compression, cardiac arrhythmia, and cardiac failure.⁷

UMBILICAL CORD STRICTURE

Cord stricture is a focal deficiency of Wharton's substance with or without vascular occlusion. It is usually seen at the fetal end of the cord and often with superimposed torsion.⁸ Most strictures are seen with macerated 6-month to 8-month fetuses. Because fetal infarction or congestion is usually absent, most strictures represent postmortem artifacts secondary to maceration that begins at the fetal end of the cord.

NUCHAL LOOPS AND OTHER ENTANGLEMENTS

Fetal cord entanglements, including nuchal loops, occur in about 20% to 25% of deliveries and are associated with cords of excessive length and male fetuses. Usually the higher the number of loops means the longer the average cord length. Nuchal cords are significantly more frequent when the placenta is posterior than when the placenta is anterior or fundal. It is not entirely clear if a long cord predisposes to fetal entanglement or if the long cord is the result of prior entanglement, fetal

movement, and excessive stretch. Looping has been identified in early gestation as well as at term.^{3,6} Long cords have been documented in 13.4% of spontaneous abortions. Nuchal cords that form early in gestation can resolve at any time or persist until term, and loops may form shortly before delivery.⁵ Tight nuchal cords can lead to fetal demise by neck compression with obstruction of jugular venous return, congestion of cerebral and meningeal vessels, and intracranial hemorrhage. A cord tightly entangled about the neck or other body part may leave a recognizable groove on the skin.

Obstruction of venous return from the placenta is associated with specific histopathological findings including (1) dilatation of fetal blood vessels in the chorionic plate with/without involvement of the stem and terminal villi, (2) fetal vascular thrombosis, (3) avascular villi, and (4) karyorrhexis (breaking down of the nucleus) in the villous stroma.⁹

MASSES OF THE UMBILICAL CORD

Masses involving umbilical cords are rare in live births and are observed in a very small proportion of stillbirths. Most frequently seen masses are hemangiomas, which present as a lobular mass involving the umbilical cord. These benign lesions are composed of vascular channels sometimes associated with myxoid degeneration. Teratomas can also present as umbilical cord masses. These are very infrequent. Cord masses are unlikely to play a significant role in the pathogenesis of stillbirth.¹⁰

ABNORMALITIES OF CORD LENGTH AND COILING

Although cord length varies, most cords at term approximately have the same length as the baby, about 55 to 60 cm. Although growth of the cord continues to and beyond term, most of the cord's length is achieved by the end of the second trimester. Cord length appears to be largely determined by genetic factors and stretch.

Short cords (< 40 cm at term) have been explained by decreased fetal movement, including uterine anomalies, mid-trimester oligohydramnios, amniotic bands, structural limb defects, functional limb defects (eg, Werdnig-Hoffman, Down syndrome), and multiple malformation syndromes.¹⁰ Long cords (> 70 cm at term) may be a consequence or a cause of associated fetal entanglements. Some observers have opined that neonates with long cords are relatively more active when compared with those having shorter cords. Cord lengths greater than 80 to 100 cm have been considered abnormally long, and been associated with knotting, torsion, encirclement around body parts, prolapse, and vascular occlusions.¹⁰

CORD COILING AND ITS ABNORMALITIES

The cord coil index is calculated as the number of coils divided by the cord length in centimeters.^{11,12} Increased umbilical cord coiling is defined as ≥ 0.3 coils/cm. It has been observed in 37% of cases of stillbirth, 14% of cases of fetal intolerance of labor, and 10% of cases of intrauterine growth restriction.^{11,12}

Decreased umbilical cord coiling is defined as ≤ 0.1 coils/cm. Reduced cord vessel coiling is also associated with similar adverse pregnancy outcomes. Decreased coiling has been observed in 29% of cases of stillbirth, 21% of cases of fetal intolerance to labor, and 15% of cases of intrauterine growth restriction.^{11,12}

MULTIPLE GESTATION

In 2005, the total twin birth rate in the United States was 32.2 twins per 1000 births.¹³ The twin birth rate has risen 70% since 1980.¹³ Twins are generally either monozygotic or dizygotic (Fig. 1). The occurrence of dizygotic twinning varies widely between populations, ranging from about 6 per 1000 in Asia to 10 to 20 per 1000 in the United States and Europe and as high as 40 per 1000 in Africa.¹³

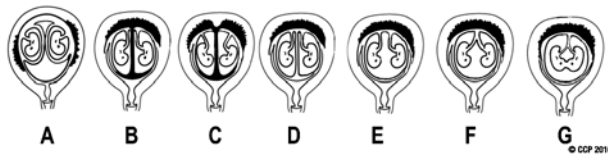


FIGURE 1. This diagram depicts the development of the dizygotic (A, B, C) and monozygotic twins (D, E, F). (With permission from Core Curriculum in Perinatal Pathology. Copyright © 2010 CCP).

There are 3 morphological patterns of twin placentas. These are diamniotic dichorionic, diamniotic monochorionic, and monoamniotic monochorionic. When a twin placenta is monochorionic, the fetuses are identical. If it is diamniotic dichorionic and the sexes of the fetuses are the same, there is a 40% chance of them being identical. If the sexes of the fetuses are different, obviously they are fraternal.

Diamniotic-dichorionic dividing membranes are thick and firmly attached to the chorionic layer of the fetal surface of the placental disc (Fig. 2). Diamniotic-monochorionic placentas have thin, translucent dividing membranes that can be removed without disrupting the fetal surface of the placenta (Fig. 3). Monoamniotic-monochorionic twinning occurs at day 8 to 10 after fertilization, accounting for 1% of all monozygotic twins pregnancies and do not have a dividing membrane.

Twin pregnancies and especially monozygotic twins are characterized by an increased incidence of both fetal and maternal complications (Figs. 4, 5).^{13,14} The majority of monochorionic twins have vascular anastomoses, and this shared blood supply can result in *twin-to-twin transfusion syndrome* (TTTS), a condition occurring in up to 15% of monochorionic diamniotic twins. TTTS results in asymmetrical fetal growth and fetal mortality in 80% or more of untreated cases, particularly if problems develop before 28 weeks of gestation. Severe TTTS is reported to occur in 5.5% to 17.5% of cases.¹⁵

Placental vascular anastomoses, unequal placental sharing, and abnormalities in umbilical cord insertions are all associated with TTTS. It is believed that almost all monochorionic twins have intertwin vascular anastomoses.^{16,17} These vascular anastomoses can be either direct, superficial anastomoses between the twins' umbilical cord branch vessels on the chorionic plate surface; or "deep" anastomoses, wherein the arterial vessels from 1 twin's cord pierce the chorionic plate of its co-twin to supply a placental cotyledon drained by the venous system; or both. Artery-to-artery and vein-to-vein anastomoses are superficial anastomoses with bidirectional flow, but artery-to-vein anastomoses are deep anastomoses with unidirectional flow from 1 twin to the other.^{16,17} It is thought that TTTS is

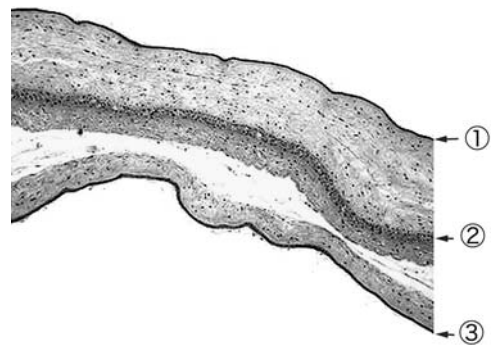


FIGURE 2. Diamniotic-dichorionic dividing membrane. Amnion layers (1, 3) and chorion layers (2). (Hematoxylin and eosin, $\times 100$).

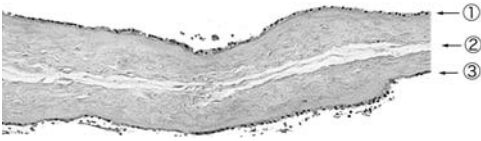


FIGURE 3. Diamnionic-monochorionic placenta has thin, translucent dividing membranes that can be removed without disrupting the fetal surface of the placenta. Amnion layers (1, 3) and chorion layer (2). (Hematoxylin and eosin $\times 100$).

more likely to develop when there is a paucity of bidirectional artery-to-artery and vein-to-vein anastomoses that can assist with regulation of intertwin circulatory imbalances. It has been suggested that artery-to-artery and vein-to-vein anastomoses are protective when present.

TWIN REVERSED ARTERIAL PERFUSION SYNDROME

In approximately 1% of monozygous twins, 1 twin has numerous malformations and an incompletely developed heart, parasitizing the co-twin’s circulation. These twins frequently do not survive.¹⁸



FIGURE 4. Monoamniotic-monochorionic twin placenta with two umbilical cords inserting into the placental disc very close to each other. The twins were in the same sac.



FIGURE 5. Monoamniotic-monochorionic placenta with entangled cords. The twins were stillborn.

EARLY AMNION RUPTURE SEQUENCE (AMNIONIC BAND SYNDROME)

Amnionic bands are thought to be redundant folds of amnion that form as the extra-amniotic space, which disappears in the early second trimester. The fetal amniotic band syndrome describes fetal abnormalities that appear as limb amputations and anencephaly-like lesions that do not follow anatomic developmental configuration. Affected fetuses are often found to have internal abnormalities of the central nervous system, gastrointestinal tract, cardiovascular system, and facial clefting. Occasionally amnionic membrane is found adherent to fetal parts.¹⁹

As not all associated defects can be explained by external physical trauma, the observation of the much higher observation of amniotic bands than the fetal syndrome and because all fetuses are exposed to amnion, the pathogenic mechanism of this syndrome remains unknown.

Examination of the Placenta in the Pathology Laboratory

Upon receipt of the placental specimen, the pathology staff should confirm the accuracy of specimen labeling and provision of appropriate clinical data. Often a timely phone call to responsible caregivers

may provide important insight as to the clinical circumstances of the stillbirth and the clinical questions at hand that may not be apparent in the written medical record or pathology order form.

Initially the specimen is examined with the attached umbilical cord and membranes. The maternal and fetal surfaces are inspected, photographed, and a description of any discrete abnormalities is made. The length and character of the umbilical cord is documented. The membranes are inspected, the site of rupture relative to the nearest placental margin is documented and a membrane roll is prepared. After trimming the umbilical cord and the membranes and draining the excessive blood, the placental disc is weighed, measured, and cut in 1 cm thick slices, starting from the maternal surface to the chorionic plate.

Abnormal Development of Chorionic Villi

There are a number of causes for abnormal development of the chorionic villi. Decreased availability of oxygen and other nutrients is a common cause of a compromised villous development. One important cause of such deprivation is underperfusion of the maternal intervillous space.

There are different patterns of abnormal villous development with compromised oxygen delivery to the placenta: *preplacental*, *uteroplacental*, and *postplacental hypoxia*.²⁰ The available oxygen levels determine the growth pattern of the capillaries. Changes in the maturation and the degree and type of fetoplacental angiogenesis determine the morphology and function of the vessels.²⁰

PREPLACENTAL HYPOXIA

Preplacental hypoxia may be associated with maternal anemia, pregnancy at high altitude, and maternal chronic hypoxia.^{20,21} In this condition, low oxygen levels induce

branching angiogenesis, resulting in clusters of richly capillarized, short, highly branched, and notched terminal villi showing increased syncytial knots (Tenney-Parker changes). The highly branched, netlike capillary beds show less flow resistance than comparably large capillary beds composed of longer, less-branched capillaries.

UTEROPLACENTAL HYPOXIA

Uteroplacental hypoxia refers to *maternal vascular underperfusion* of the intervillous space and is usually related to either structural abnormalities of the uterine spiral arteries or maternal vascular disease. The classic example of uteroplacental hypoxia is pregnancy-induced hypertension and preeclampsia in which the placenta sustains reduced maternal perfusion. Maternal vascular underperfusion is an important cause of fetal growth restriction, preterm rupture of membranes, and preterm labor.^{20,21} In its most severe form, it can be associated with stillbirth and life-threatening maternal conditions such as eclampsia, abruptio placentae, cardiopulmonary failure, and disseminated intravascular coagulation.

The principal pathological changes of the placenta in preeclampsia are: *decidual vasculopathy*, *parenchymal infarcts*, *abruptio placentae*, *abnormal villous development*, and *growth impairment*.^{20,21} These pathological features may not correlate with the clinical disease. These lesions may be found in other disorders such as lupus anticoagulant and as maternal genetic and acquired thrombophilias. They are, however, indicative of abnormal uteroplacental perfusion. Table 3 summarizes placental abnormalities that compromise the growth of the fetus.

DECIDUAL VASCULOPATHY

The villous and intervillous lesions seen with maternal underperfusion are believed to be the result of early developmental events that lead to inadequate vascular remodeling, and/or structural

TABLE 3. Placental Growth Disorders That Lead to or Are Associated With Fetal Growth Restriction

Abnormal umbilical insertions (circumvallate, velamentous)
Abruption (chronic, partial)
Avascular villi (fetal vascular thrombosis)
Maternal decidual vasculopathy
Fibrin/fibrinoid deposition with cytotrophoblast hyperplasia, septa and basal plate
Infectious villitis
Villous (parenchymal infarcts)
Multiple gestation (limited endometrial surface area, vascular anastomoses)
Triploidy and other aneuploidies
Placenta previa

abnormalities of maternal arteries.²² These structural abnormalities include mural hypertrophy of arterioles in the uterine decidua and persistent muscularization of arteries in the basal plate. Any artery not remodeled by endovascular trophoblast may undergo fibrinoid necrosis morphologically resembling acute atherosclerosis in association with the late clinical phase of preeclampsia.

Findings related to abnormal implantation include immature extravillous trophoblast and increased placental site giant cells. Longstanding maternal vascular underperfusion results in increased syncytial knots, villous agglutination, and intervillous fibrin deposition.²³

These lesions are not only found in preeclampsia but also in normotensive pregnancies complicated by fetal intrauterine growth restriction or associated with maternal thrombophilic conditions.²⁴

VILLOUS (PARENCHYMAL) INFARCTS

Villous infarction is caused by inadequate maternal blood supply to the intervillous space, seen in maternal conditions such as hypertension, particularly preeclampsia, maternal diabetes mellitus, and systemic lupus erythematosus.²⁴

Microscopic features are obliteration of the intervillous space with villous crowding. Early infarcts show congested, sometimes hemorrhagic villi. Necrotic changes include pyknosis and karyorrhexis of trophoblast with eventual loss

of trophoblast structure. Chorionic villi surrounding the infarct show prominent syncytial knots.^{3,8,13}

INTERVILLOUS (INTRAPLACENTAL) THROMBI

Intraplacental hematomas are localized, circumscribed clots in the intervillous space. Generally they are small (1-2 cm), and have been identified in 45% of placentas. Although most of the blood in a hematoma is maternal, most hematomas appear to form at the site of a leak in the fetal circulation, which causes the adjacent maternal blood to form an expanding clot.²⁴ Fetal anemia, fetal organ damage, hydrops, growth restriction, and death are associated with this placental finding.²⁴ When hematomas are numerous or large, they may be associated with significant fetal-maternal hemorrhage. Intraparenchymal placental hematoma should be distinguished from those of the intervillous space, identified as subchorial hematomas or due to placental abruption.

PLACENTAL ABRUPTION (RETROPLACENTAL HEMATOMA)

Retroplacental hematomas are clots, recent or chronic, situated in the decidua between the placental floor and the muscular wall of the uterus, findings supporting the pathological diagnosis of abruption. The same term is used for both histological observation and clinical event of maternal pain and bleeding; causing

confusion at times in identifying causes of stillbirth.

A study of 7.5 million singleton births delivered in 1995 and 1996 in the United States, identified abruption in 6.5 per 1000 births with an associated perinatal mortality rate of 119 per thousand births.²⁵ The high mortality with abruption was due, in part, to its strong association with preterm delivery; 55% of the perinatal deaths with abruption were due, in part, to premature birth.²⁶

Smaller, more localized retroplacental hematomas are easily overlooked unless the placenta is sliced carefully after 24 hours of formalin fixation. Recent clots are dark red, like the placenta, but the texture is more firm and solid. The region of the clot may not be apparent on the affected maternal surface, which can be flat like the rest of the maternal surface, but cut sections show compression of the overlying placenta. Older retroplacental hematomas are firm, have a brownish color, and the overlying placenta is usually infarcted, especially if the hematoma is large. Old hematomas are gray or white. They are occasionally associated with acute deciduitis, sometimes even with microabscesses in the basal plate.

Intravillous hemorrhage occurs when the villous capillaries are injured and ruptured. Usually the villous parenchyma surrounding infarction and blood clot shows intravillous hemorrhage.²⁷

Hemorrhages at the margin between the placenta and membranes are generally less disruptive of the placental-uterine attachment allowing chronic changes in the placenta. Small hematomas in the decidual layer that occur days or weeks prior to delivery, sometimes in association with a circumvallate placenta are diagnosed histologically as *chronic abruption*.²⁸ This association is confirmed by membrane hemosiderin and a clinical history of chronic vaginal bleeding. Chronic abruption is significantly associated with oligohydramnios and premature birth.²⁸

PERIVILLOUS-INTERVILLOUS FIBRIN DEPOSITION

Perivillous fibrin deposition is a common finding. Small, grossly identifiable clumps of perivillous fibrin are common and usually innocuous.²⁹ Fox found them in 22% of full-term placentas.³⁰ Accumulations sufficient to affect placental function are less common, usually centrally located, and involve about one-fourth of the placental mass and commonly associated with fetal growth restriction and stillbirth. These larger lesions are termed placental floor infarction. Andres et al³¹ found 30 maternal floor infarcts in a series of 32,182 placentas (0.09%), whereas Naeye³² found 0.5% in the Collaborative Perinatal Study. The combined prevalence of maternal floor infarct and massive fibrin deposition, as defined more restrictively by Katzman and Genest³³ was 0.005%.

POSTPLACENTAL HYPOXIA

Postplacental hypoxia is seen with intra-uterine growth restriction associated with absent or reversed end-diastolic umbilical flow. Postplacental hypoxia represents a late stage of chronic maternal underperfusion in which longstanding hypoxia causes placental structural abnormalities that restrict fetal perfusion of the placenta. In postplacental hypoxia, both maternal and fetal perfusions of the placenta are decreased, but the latter can predominate leading to paradoxical intervillous hyperoxia. This hyperoxia may lead to additional villous damage due to the production of oxygen free radicals.³⁴ In this situation, there are relatively high oxygen levels, which induces nonbranching angiogenesis resulting in poorly developed, long, slender, or filiform terminal villi with minimal branching, minimal syncytial knots, and long, largely unbranched capillary loops called *terminal villous hypoplasia*. These placentas are markedly small, often less than the third centile for gestational age.

TERMINAL VILLOUS IMMATUREITY WITH PLACENTAL OVERGROWTH (DELAYED VILLOUS MATURATION)

Terminal villous immaturity is the increase in number of large distal (terminal) villi with abundantly proliferated capillaries, stromal macrophages, and interstitial fluid, which is uniformly distributed throughout the villous stroma. This growth pattern is most commonly seen with gestational diabetes. The phenotype may reflect maternal hyperglycemia leading to fetal hyperinsulinemia. Insulin binds to placental insulin and insulin-like growth factor receptors, stimulating accelerated fetoplacental growth. Placentas from patients with *Beckwith-Wiedemann syndrome* (exophthalmos, macroglossia, gigantism) often show similar findings attributable to their known increase in insulin-like growth factor-II expression. Fetal and placental overgrowth in pregnancy complicated by gestational diabetes, increases the risk of stillbirth.³⁴

Infection of the Fetal Membranes, Cord, and Placenta

MATERNAL INFLAMMATORY RESPONSE

Because the maternal response to infection manifests itself in the chorionic plate and chorioamniotic membranes, these sites have been named “the maternal compartment.” Inflammatory cells of maternal origin infiltrate these tissues, generally in response to microbial infection. Though generally the result of ascending infection,^{35,36} intrauterine infections may be due to spread from a contiguous infection or hematogenous in origin.³⁷

Acute chorioamnionitis is a condition characterized by the presence of polymorphonuclear leukocytes in the placental membranes. Necrosis of the amnion indicates a more severe process. Clinically diagnosed chorioamnionitis does not correlate

well with histological chorioamnionitis or culture positive amniotic fluid.

FETAL INFLAMMATORY RESPONSE

The umbilical cord, including its vessels, the Wharton’s substance surrounding them, and fetal blood vessels in the chorionic plate has been named as the “fetal compartment.” It is in these tissues that the fetal response to infectious is manifested.^{38,39} Acute *funisitis* is defined by the presence of polymorphonuclear leukocytes in the Wharton’s substance. In the more advanced stages, the inflammatory cellular infiltrate involves the arteries and the vein causing arteritis and phlebitis. At the end stage, necrotizing funisitis and concentric umbilical perivasculitis (subacute sclerosing funisitis) can be seen. The latter comprises degenerating neutrophils and eosinophilic debris and form concentric circles around 1 or more umbilical vessels. It is seen in long-standing bacterial, fungal, protozoal, and viral infections.

Sometimes the acute inflammation involving the fetal blood vessels triggers intravascular thrombi that might cause obstruction of the vessels. This finding markedly worsens the outcome of acute chorioamnionitis and is associated with fetal death.

The amniotic fluid infection syndrome is defined as inflammation involving both fetal and maternal compartments and presence of polymorphonuclear leukocytes in the fetal bronchial tree and gastrointestinal tract.^{38,39} Positive fetal blood or lung bacteriological cultures are confirmatory. However, some fetal bacterial infections (group B Streptococci) may cause lethal fetal infection without eliciting significant inflammatory reaction.

INFECTIOUS PLACENTITIS

Acute Placentitis

Acute placentitis is diagnosed if polymorphonuclear leukocytes are identified in the chorionic villi and the intervillous

space and the process involves more than 50% of the organ.⁴⁰ Frequently the chorionic villi form clusters by fusing to each other. In severe cases, necrosis causes villous and intervillous abscesses.

Certain bacteria and viruses characteristically cause acute placentitis. *Listeria monocytogenes* is one bacterium that forms a pathognomonic histological picture of numerous parenchymal microabscesses. Though the reported incidence of human listeriosis in pregnancy is only 12 per 100,000, infections may occur in clusters and the detection of 1 case may be a harbinger for others in the same community, generally related to the same contaminated food source. *Campylobacter fetus*, *Chlamydia psittaci*, *Francisella tularensis*, and *Coccidioides immitis* also cause placentitis. *Escherichia coli* and group B streptococcus can cause acute villitis and intervillitis with varying degrees of necrosis. Acute placentitis is highly associated with fetal death.

CHRONIC PLACENTITIS

Chronic placentitis is characterized by diffuse histiocytic villitis, fibrosis, and clustering of the chorionic villi and in later stages mineralization. During the early phases there is diffuse edema and fetal erythroblastemia. There may be plasma cells in the basal plate.⁴⁰ Cytomegalovirus (CMV), toxoplasma, *Treponema pallidum* or similar organisms can cause chronic placentitis. Ninety percent of cases in the United States are due to CMV or *T. pallidum*. Worldwide, the most common cause is malaria.⁴⁰ In congenital syphilis there is a predominantly histiocytic chronic villitis, proliferation of Hofbauer cells, proliferative endovasculitis, stem villous perivasculitis with concentric mural vascular sclerosis, and necrotizing umbilical periphlebitis. In congenital CMV infection, the placenta is large and pale or can also be small and fibrotic. Both patterns have 3 important features: prominent villus fibrosis and mineralization,

plasma cell infiltrates in the villous stroma, and diagnostic large intranuclear inclusions with or without smaller basophilic cytoplasmic inclusions. Infection with any of the 4 microbes may be associated with fetal growth restriction, anatomic abnormalities, and death.

Idiopathic (Noninfectious) Villitis

Villitis of unknown etiology (VUE) is a common lesion occurring in approximately 3% to 5% of all term placentas.⁴¹⁻⁴³ No causative organisms have been identified and no maternal infectious symptoms have been described. VUE lacks many features of chronic infectious placentitis. Areas of villous inflammation are distributed in a nonuniform fashion. It represents a maternal immune response occurring within the fetal tissue.⁴² The infiltrating maternal cells are primarily CD3-positive T lymphocytes. It is the most common placental lesion identified in nonhypertensive term pregnancies with significant fetal growth restriction. Although VUE has been described in early spontaneous losses, it is not found with increased frequency in stillbirth cases.⁴³

CHRONIC HISTIOCYTIC INTERVILLOSITIS

Chronic histiocytic intervillitis is a diffuse infiltration of the intervillous space by CD 68-positive monocyte and macrophages, accompanied by variable degrees of perivillous matrix type fibrinoid (a fibrin-like protein with histochemical properties seen in the matrix of different types of tissues. It is accepted to be produced by extravillous trophoblast proliferating in the septa and basal plate.⁴¹⁻⁴³ Chronic histiocytic intervillitis is commonly seen in recurrent spontaneous abortions, intrauterine growth restriction, and stillbirth. Overall perinatal mortality rate is extremely high (77%) and only 18% of all pregnancies in the affected mothers reach the third trimester.⁴³ Placentas are often small for gestational age.

It may represent an inappropriate expression of adhesion molecules on the extravillous trophoblast.

Lesions Associated With Compromised Maternal and Fetal Circulation and Hematological Disturbances

SUBCHORIAL HEMATOMAS (BREUS MOLE)

Laminated subchorionic thrombi form in small quantities regularly in the subchorionic space. It is at this site where the intervillous (maternal) blood is deflected backward and eddying of intervillous blood accounts for the small amounts of fibrin that normally accumulates here.

Recent subchorial hematomas are dark red and may have a laminated appearance. Older lesions evolve through shades of brown to gray and white as the hemoglobin degrades. Mature lesions appear as white patches or plaques of fibrin and laminated clot under the chorion. They often cause bosselation of the fetal surface of the placenta.⁴⁴ The fibrin accumulations normally increase with maturation. However, greater amounts of this material may accumulate underneath the chorion in some abnormal placentas, forming distinct subchorionic hematomas, which may measure up to 15 cm in diameter. Massive clots, which significantly distort the placental architecture by displacing the villi and forming an expansile mass, often extend the full thickness of the placenta, from the chorionic plate to the decidua basalis. This may markedly reduce placental function, resulting in fetal death in the second and third trimesters.⁴⁴ Subchorionic hematomas may be associated with maternal inherited thrombophilias.⁴⁴ They have been associated with preterm delivery, spontaneous abortion, vaginal bleeding, elevated alpha-fetoprotein levels, intrauterine growth restriction,

and mid-trimester and late-term fetal death. They are more often found when maternal circulatory disorders exist such as complex heart disease, and with maternal antinuclear antibodies and thrombophilias.

BASAL PLATE FIBRIN DEPOSITION (MATERNAL FLOOR INFARCT)

In this condition, a band of dense fibrin of varying thickness is seen on maternal surface (basal plate). It is usually yellow and firm to palpation. On microscopic examination with routine stains (hematoxylin and eosin), it appears as a smooth, homogeneous, and pink substance⁴⁵ and sometimes associated with massive perivillous fibrin deposition. Necrotic villi can be seen enmeshed in the basal layer of acellular fibrin. This process may extend into the parenchyma. The cause is undetermined. It has been associated with recurrent poor pregnancy outcome, particularly mid-trimester losses and intrauterine growth restriction.⁴⁵

Compromised Fetal Circulation

THROMBOSIS INVOLVING THE FETAL VASCULATURE (FETAL THROMBOTIC VASCULOPATHY)

Occlusive thrombi in branches of the umbilical arteries, tributaries of the umbilical vein on the placental surface, and stem vessels in the stem villi within the placenta produce changes in fetal tissue downstream to the thrombi.⁴⁶⁻⁴⁸ The changes appear as wedge-shaped areas of pale pink or gray-tan tissues, which correspond, to collections of avascular villi. These lesions originally were named fetal thrombotic vasculopathy but a more precise term “thrombosis of fetal vasculature” has replaced the original term. Extensive lesions involving 40% to 60% of the placental mass are viewed as causative of fetal death. Thrombosis of fetal vasculature is usually associated with hypercoagulable states in the fetus.

In some instances, coagulopathic conditions combine with other factors, such as vascular anomalies, local trauma or stasis in velamentous vessels, or amniotic fluid infection, to produce fetal thrombosis.⁴⁹

VILLOUS EDEMA (HYDROPS PLACENTALIS)

Villous edema involving the chorionic villous stroma has been ascribed to hypoxic/ischemic placental injury.^{50,51} Extensive and diffuse edema is called *hydrops placentalis*.

Placental and/or fetal hydrops complicates 1 out of 3000 pregnancies.^{52,53}

Common known causes are twin-twin transfusion syndrome, infections that cause placentitis, aneuploidies such as Turner syndrome, and congenital heart disease. Diffuse villous edema is highly associated with fetal mortality because of underlying associated fetal disorders and its adverse effect on placental function.

Summary

Placental lesions identified in stillborn are of clinical interest and frequently involved as having a causal role without sufficient objective evidence. The majority of the literature dealing with stillbirth is descriptive. Currently placenta and umbilical cord lesions associated with stillbirth can be divided into five groups. These are (1) macroscopic lesions of the placental disc, umbilical cord and membranes, (2) complications of multifetal placentation, (3) abnormal development of the villous parenchyma, (4) infection and (5) compromise of the maternal and/or fetal circulation and hematological disturbances. Currently a significant number of these events that have been described in stillbirths, only a few can be characterized as real “causes” of demise. Some of these are disruption of velamentous vessels, total obstruction of the umbilical cord, massive fibrin deposition involving the entire placental parenchyma, abruptio, hydrops placentalis from various causes

and complications of multifetal gestation such as TTTS and twin-reversed arterial perfusion sequence. Additional studies of sufficiently large cohorts with appropriate controls are needed to establish the causal relationships with other lesions.

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