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Original Review

Comprehensive Review of the Stillborn Placenta

CEU

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Stillbirth is a common complication of pregnancy, affecting one in every 160 women in the United States who are pregnant. Stillbirth has a significant adverse medical and psychological impact on families. Identifying the cause of stillbirth can yield recommendations for the management of future pregnancies, provide a risk of recurrence, and give families a sense of closure. The placental examination is one component of a comprehensive stillbirth investigation. A systematic approach to the examination of the placenta is presented, along with an explanation of critical findings that have been associated with stillbirth. A checklist for placental evaluation by the provider who attends the birth is provided, along with information on stillbirth assessment programs.
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INTRODUCTION

The intrauterine death of a fetus is a tragic and unfortunately common complication of pregnancy. Approximately 3 million stillbirths occur every year worldwide, with more than 90% of these cases occurring in developing countries.[1] In the United States, approximately 26,000 stillbirths occur yearly.[2] Despite technological advances in medical care, the stillbirth rate in the United States is higher than other developed countries.[3] The stillbirth rate (fetal death at 20 weeks' gestation or later) in the United States declined by an average of 1.4% per year from 1990 to 2003; however, the rate has remained stagnant since 2003.[4] A decline in neonatal deaths, attributed to the advanced care of the preterm neonate, and a constant stillbirth rate has resulted in the number of stillbirths surpassing the number of neonatal deaths in the United States.[5]

Although risk factors for stillbirth have been identified, the specific cause of stillbirth often remains elusive.[6] Contributing and/or causative factors of stillbirth may be determined via a review of the maternal medical and obstetric history, fetal autopsy, and placental examination. However, less than half of stillbirth cases undergo autopsy.[7]

An examination of the placenta is more widely accepted by families due to its noninvasive nature, and many causes of stillbirth can be identified by gross examination of the placenta in the birth room. Birth attendants should be comfortable with examination of the placenta because this examination is a key opportunity to contribute to the identification of the cause of the stillbirth. In this article, we review a systematic approach to the evaluation of the placenta, with particular focus on features that may indicate the etiology of stillbirth.

BACKGROUND

Definitions of Stillbirth

Variations in the definition of stillbirth have unfortunately resulted in inconsistent data reporting and confusion among practitioners. Several terms have been used to define stillbirth, including fetal death, fetal demise, fetal loss, and stillborn.[8] Fetal death can occur at any gestational age; however, the gestational age threshold used to define fetal death in epidemiologic reports ranges from 18 to 28 weeks' gestation. In the United States, the definition of stillbirth also varies from state to state. The American College of Obstetricians and Gynecologists' definition of stillbirth is the birth of a fetus at 20 weeks' gestation or more or at a weight 350 g or higher that shows no signs of life.[9] This definition is used by most but not all states and the Centers for Disease Control and Prevention (CDC) because it represents the 50th percentile for fetal weight at 20 weeks' gestation.[9] Other institutional definitions may have a more advanced gestational age or include Apgar scores or physical examination findings.[1,2,10,11] The CDC calculates a fetal mortality rate as the number of fetal deaths at 20 weeks' gestation or more per 1000 live births, plus fetal deaths at 20 weeks' gestation or more; the denominator thereby representing the population at risk. In 2012, the fetal mortality rate was 6.05 per 1000 live births.[12]

Evaluation of Stillbirth

To standardize the approach to stillbirth evaluation, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) initiated the Stillbirth Collaborative Research Network (SCRN) in March 2006; enrollment was completed in September 2008. Additional goals of the study were to determine the incidence of stillbirth based on geographic location and identify risk factors for stillbirth.[13] The SCRN conducted a prospective, multicenter, population-based, case-control study of stillbirths at 5 academic centers.[14] These efforts resulted in the publication of more than a dozen articles, which have added to our knowledge about the potential causes of stillbirth and evidence-based management of stillbirth.

The SCRN sought to establish standards for the determination of probable cause, possible cause, and those that are present but not necessarily causal of stillbirth.[15] A probable cause has a high likelihood of directly causing the fetal death (eg, diabetic ketoacidosis). A possible cause is not

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Quick Points

- Gross examination of the placenta should be performed after the birth of a stillborn fetus.
- Examination of the placenta can contribute to identification of the etiology of the stillbirth and can potentially provide immediate feedback to the family.
- Stillbirth assessment programs use expertise from several fields of medicine (obstetrics, pediatrics, pathology, genetics) to investigate the cause of stillbirth.

a direct cause of stillbirth but is possibly involved in a pathophysiologic sequence that led to the fetal death (eg, type 1 diabetes with elevated hemoglobin A1c). A condition that does not meet probable or possible criteria is classified as present (eg, gestational diabetes).[13] For the study, detailed protocols for the placental and umbilical cord examination, placental pathology, fetal postmortem examination, and medical record abstraction and maternal interview were developed. Among 512 cases reviewed, a probable cause was identified in 60%, and one or more possible causes were identified in 76.2%. Placental disease was the most common cause of stillbirth at 24 weeks' gestation or greater.[4]

Why Examine the Placenta?

The placenta is one of the most important reproductive structures; it is responsible for the provision of nutrients and oxygen to the fetus and subsequently the removal of fetal waste products.[16] In a review of 104 perinatal deaths between 2004 and 2008, placental examination by itself could identify the cause of fetal death in 48% to 51% of cases, and a placental finding could explain the cause of death in 69% of stillbirth cases.[17] These findings coincide with other reviews reporting 35% to 88% of stillbirth cases having placental findings causative of death.[17,18]

An examination of the placenta is recommended as part of the stillbirth evaluation by several professional groups.[7,19,20] The American College of Obstetricians and Gynecologists guidelines for stillbirth evaluation include a thorough maternal medical and family history, focused laboratory evaluation, fetal autopsy, examination of the placenta, and chromosomal microarray analysis.[9,21] Despite these recommendations, the examination of the placenta is underutilized.[17] In a 2007 review, the placenta was examined in less than half of the births in which placental examination was clinically indicated.[22] The underutilization of the placental examination has been attributed to lack of perinatal pathologists and a lack of a standardized approach to the stillbirth evaluation.[2]

During the gross inspection of the placenta, 3 of the 5 senses are utilized: sight, touch, and smell. In the following text, we describe major anatomic features that can be visualized and describe their association with stillbirth. A summary of key placental features is provided in Table 1. After completion of the gross placental examination, normal and abnormal findings are recorded in the woman's chart. Reference to the placental examination is invaluable to future investigations and counseling on the cause of stillbirth.

COMPONENTS OF THE PLACENTAL EXAMINATION

Placental Disc

Size

A term placenta is disc-shaped, weighs approximately 450 to 650 g, and measures 15 cm in diameter.[23] The placental weight can be obtained and compared to normal values for gestational age.[7] A large placenta (> 750 g) is associated with maternal diabetes mellitus, polyhydramnios, and infection. A large placenta that is also pale and edematous is suggestive of fetal hydrops. A small placenta (< 450 g) is associated with maternal vascular diseases, fetal infections, fetal malformations, and fetal aneuploidy.[23] A small placenta is often seen in cases of fetal growth restriction. The decreased total surface area available for oxygen and nutrient exchange that occurs with a small placenta has been suggested as one possible etiology for fetal growth restriction.[16]

Structure

After birth, the placenta may be immediately assessed for intactness. The maternal surface is divided into approximately 20 irregular lobules or cotyledons.[24] Missing cotyledons are suggestive of retained products of conception and can be a cause of postpartum hemorrhage. Retained products are more common after the birth of a stillborn fetus. In a recent review by Endler et al, women who had a stillbirth had an increased risk for retained placenta when compared to women with live born neonates, 5.8% versus 2.16% (odds ratio [OR], 2.29; 95% confidence interval [CI], 2.18-3.56).[25] If the birth attendant has suspicion for retained products of conception, sonographic imaging of the uterine cavity can be considered for further evaluation.

The presence of accessory lobes is documented. Accessory lobes are attributed to localized failure of the capsular villi to atrophy.[23] In abnormal lobation, the main placental disc is connected to the accessory lobe by velamentous vessels. The velamentous vessels are not protected by Wharton's jelly or the placental parenchyma and are at increased risk for rupture and thrombosis, events which could lead to fetal morbidity or mortality.[23]

Lesions on the Fetal Surface

The fetal surface faces the amnionic cavity and has a glossy appearance.[24] A placental hemangioma (chorioangioma) is a circumscribed, purple-red mass composed of proliferating

Table 1. Placental Findings and Associated Diagnoses

Finding	Differential Diagnosis
Placental Disc	
Size	
Large (≥ 750 g)	Maternal diabetes, hydrops, polyhydramnios, fetal or maternal anemia, infection
Small (< 450 g)	Maternal vascular disease, fetal aneuploidy, fetal infections, fetal malformations
Retroplacental hematoma	Maternal cocaine use, chorioamnionitis, maternal trauma, preeclampsia, Hemolysis, elevated liver enzymes, low platelets syndrome, maternal cigarette use
Infarct	
Central	Maternal vascular disease, Rhesus incompatibility, lupus anticoagulant, cocaine use
Peripheral	Normal, live birth
Abnormal lobation	
Hemangioma (5 cm)	Congestive heart failure, fetal growth restriction, placental abruption
Umbilical Cord	
Two-vessel cord	Intrauterine growth restriction, fetal aneuploidy, congenital anomalies
Abnormal insertion	
Velamentous	Multiple gestation, abnormal placental lobation, single umbilical artery, congenital anomalies
Marginal	Multiple gestation
Furcate	Multiple gestation
Torsion	Multiple gestation, long umbilical cord.
Stricture	Multiple gestation, long umbilical cord, deficiency of Wharton's jelly
Abnormal length	
Long (> 70 cm)	Polyhydramnios, cord prolapse, cord entanglement, cord torsion
Short (< 32 cm)	Fetal growth restriction, congenital malformations, congenital myopathies, umbilical cord rupture, intrapartum distress
Knots	
True knot	Increased fetal movement, multiparous women, male fetus, monoamnionic twins, polyhydramnios, fetal growth restriction
False knot	Varicosity that has no clinical significance
Loops/Entanglements	Monoamnionic twins, long umbilical cord
Abnormal coiling	
Hyper- (≥ 0.3 coils/cm)	Increased fetal movement.
Hypo- (≤ 0.1 coils/cm)	Decreased fetal movement
Funisitis	Chorioamnionitis, fetal inflammatory response
Multiple Gestation	
Chorionicity/amnioncity	
Monochorionic-monoamniotic	Abnormal cord insertion, cord entanglement, cord prolapse
Monochorionic-diamniotic	Abnormal cord insertion, twin-twin transfusion syndrome
Dichorionic-diamniotic	Abnormal cord insertion, placental fusion

vessels that appears as a bulge on the fetal surface.[24] Placental hemangiomas occur in 1% of normal placentas and are benign; however, fetal death can develop secondary to congestive heart failure, placental abruption, or growth restriction if the size is bigger than 4 cm in diameter.[26] Such complications are due to sequestration of blood within the hemangioma.[24]

Lesions on the Maternal Surface

The maternal surface of the placenta is inspected for calcium deposits, hematomas, and infarcts. Calcium deposits are commonly observed on the maternal surface of normal term placentas and are considered a normal part of placental aging.

These deposits are fine, white to yellow, and have a gritty texture.[24] They are of no clinical significance if seen in a term placenta. Calcium speckling identified in a placenta from a fetus at less than 32 weeks' gestation, however, has been associated with low birth weight, low Apgar scores, and neonatal death.[27] Calcium deposits in a preterm placenta may be the result of ischemia-related metastatic process.

A hematoma on the maternal surface may indicate placental abruption as a cause for fetal demise. Placental abruption can be identified as a retroplacental hematoma located between the placental floor and uterine wall (Figure 1). A retroplacental hematoma that covers more than 50% of the placental surface is associated with a higher risk of fetal death. In a 2014 review of placental findings among singleton stillbirths, Pinar et al identified a retroplacental hematoma in 23.8% of stillbirths and 4.2% of live births ($P < .001$).[28] However, when analyzed by gestational age, a retroplacental hematoma was more common in placentas obtained from a stillbirth that occurred at a later gestational age. At less than 24 weeks' gestation, a retroplacental hematoma was identified in an equal number of stillbirths and live birth placentas (36.2% and 36.6%, respectively).[28] The timing of the placental abruption can be inferred by its color. An acute clot will initially appear dark red and then progress to a brown-yellow-orange color, eventually becoming white over time.

Placentas obtained from live births are commonly characterized by infarcts at the periphery; however, centrally located infarcts are associated with stillbirths.[3] An infarct is an area of villous ischemic necrosis attributed to inadequate maternal blood supply to the intervillous space.[3,23] Infarcts associated with a stillbirth typically encompass the entire thickness of the placenta, have a lobular configuration, and are outlined by a distinct border. Placental infarcts are initially red, firm, and indurated; however, with time they will progress to a yellow-white color and eventually become more granular and solid.[19] A minor infarction represents less than 5% to 10% of the placenta and is clinically insignificant.[23] An extensive infarction involves more than 30% of the placenta, is larger than 3 cm in diameter, and is associated with a higher risk of fetal death.[23] These clinically significant infarctions may be secondary to maternal vascular disorders (hypertension and preeclampsia), lupus anticoagulant, Rhesus incompatibility, and cocaine use.[23]

Amnion

Color

The amnion is normally translucent and purple to steel-blue.[24] The amnion of a stillborn placenta typically has a dusky pink discoloration.[24] A greenish appearance of the amnion can occur if the fetus passes meconium in utero. Meconium-stained fluid is observed in 12% of all births.[29] In a review of 37 stillbirth cases, Chang et al identified meconium-stained fluid in 49%.[30]

Typically, the fetus does not pass meconium before 36 weeks' gestation, and its presence may be indicative of a nonreassuring fetal status.[23,31] Meconium is a noxious material, and exposure to it for 12 or more hours increases the risk of fetal asphyxia.[16] Meconium has a direct toxic effect on the smooth muscle of the umbilical cord vasculature.[16] Vascular wall damage (myonecrosis) results in a flaccid vessel and blood flow to the fetus is impeded. If gentle wiping of the amnion is performed and green staining persists, it is likely that meconium passage occurred more than 12 hours before birth.[3] A brownish or yellow-brown discoloration of the amnion is indicative of old blood and can be identified in placentas that are also complicated by a retroplacental hematoma.[24]

Inflammation of the amnion (chorioamnionitis) will result in the appearance of opaque or possibly green-yellow membranes. Adherent, purulent material may be present in chorioamnionitis; and in severe cases, the amniotic epithelium may necrose and slough.[23] In these severe cases, a foul odor may also be noted.[24] Chorioamnionitis is typically associated with ascending bacterial infections such as *Mycoplasma*, *Gardnerella* and Group B streptococcus, and less commonly with fungal or viral infections. Fetal death in the setting of chorioamnionitis is attributed to sepsis, which results from the hematogenous spread of bacteria to the fetus through superficial chorionic vessels.[23] In a 2014 review, Pinar et al identified chorioamnionitis as the most common placental finding among 518 stillbirths (30.4%).[28] Caution in attributing fetal death to chorioamnionitis is advised because histologic findings without associated clinical symptoms of chorioamnionitis are relatively common and observed in 11.4% to 57.3% of term placentas.[23]

Lesions

Amnion nodosa are white-yellow, 1- to 2-mm nodules that can be easily removed from the fetal membranes. These nodules can be identified in the examination of a placenta in which the pregnancy was complicated by marked oligohydramnios.[3] The amnion is maintained by amniotic fluid; therefore, in the absence of amniotic fluid, the amnion degenerates. Amnion nodosa represent the precipitation of vernix caseosa and are composed of desquamated fetal epithelial cells, fibrin, and hair.[23,24] Oligohydramnios or anhydramnios can occur if the fetus has a structural abnormality such as bladder outlet obstruction or if pregnancy complications such as preterm premature rupture of membranes or twin-twin transfusion syndrome (TTTS) are present.[24] Oligohydramnios that occurs early in gestation may be associated with lethal pulmonary hypoplasia.

Distinct from amnion nodosa are dull-white plaques that represent squamous metaplasia. Squamous metaplasia represents maturation of the placenta and has an irregular, patch-like pattern.[24] Unlike amnion nodosa, squamous metaplasia is firmly adhered to the fetal membranes.[23] These macules are identified in 60% of normal term gestations and are typically identified at the cord insertion site.[23,24]

Amniotic bands have an unknown pathogenesis; however, they have been attributed to redundant folds of amnion or rupture of the amnion prior to fusion with the chorion.[3,24] They rarely have been observed following trauma or an amniocentesis. Amniotic bands cause disruptions of fetal growth and can result in a variety of abnormalities that resemble amputations and clefting. Entanglement or constriction of the umbilical cord by an amniotic band can lead to fetal death.[24] The diagnosis of amniotic bands can only be made by examination of the fetus and/or placenta. Amniotic bands appear as fine, delicate tissue bands on the fetal surface of the placenta.[23]

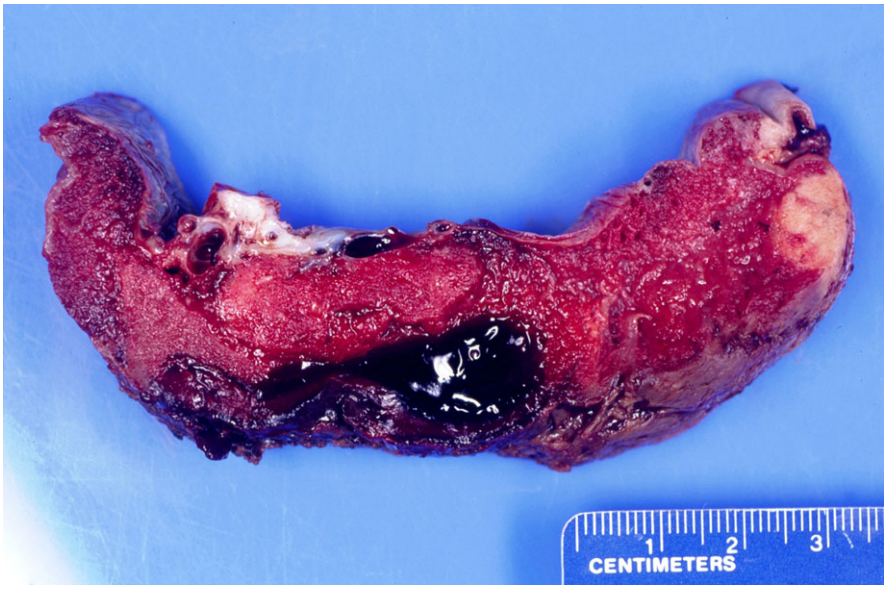

Figure 1. Excavating Hematoma Consistent with Abruption

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Umbilical Cord

Number of Vessels

There are normally 3 vessels within the umbilical cord, 2 arteries and one vein surrounded by Wharton's jelly, which is an acellular tissue composed of fibroblasts and macrophages and serves to protect the arteries and vein from compression.[24] The complete absence of Wharton's jelly has been identified as a cause of fetal death in a handful of case reports.[32,33] A 2-vessel cord, comprised of one artery and one vein, is observed in 0.5% to 1% of singleton pregnancies and 3.5% to 7% of twin pregnancies.[34] The number of vessels can be easily demonstrated after birth at the site of cord transection. The presence of a single umbilical artery has been associated with poor obstetric outcome.[35] In 2000, Rinehart et al characterized 27 pregnancies antenatally diagnosed with a single umbilical artery. Of the 6 cases with an isolated finding of a single umbilical artery, 50% were growth-restricted.[34] In contrast, Bombrys et al compared 255 pregnancies complicated by a single umbilical artery with 289 controls and demonstrated no difference in the rate of small for gestational age or fetal death with a single umbilical artery.[36] Most recently, Pinar et al (2014) reviewed the placental findings of 518 stillbirths and 1,200 live births. Single umbilical artery was identified in 7.7% of stillbirths and 1.7% of the live births (OR, 4.80; 95% CI, 2.67-8.62).[28]

Length

The length of an umbilical cord at term can be variable. The average cord length is 37 cm; however, it can range from 0 cm (achordia) to 100 cm.[23] A shortened umbilical cord (< 32 cm) has been associated with intrauterine growth restriction, intrapartum distress, umbilical cord rupture, and notably a 2-fold increased risk of death.[37] Shortened umbilical cords can be identified in a fetus affected by an abdominal wall defect such as omphalocele or limb-body wall defect. A long cord (> 70 cm) has been associated with polyhydramnios, cord prolapse, cord entanglement, cord torsion, nonreassuring fetal status, and perinatal mortality. The length of the umbilical cord can be influenced by the presence of movement disorders in the fetus. For example, shortened umbilical cords have been found in fetuses with a fetal akinesia deformation sequence and other congenital myopathies (eg, congenital myotonic dystrophy).[38]

Coiling

The umbilical cord is a helical structure that can be observed for the degree of coiling. Hyper- and hypocoiling have been described. The umbilical coiling index can be determined by the total number of complete vascular coils divided by the total length of the umbilical cord in centimeters.[39] Cord coiling measurements are obtained from a segment at least 5 cm in length.[2] Hypercoiling is defined as 0.3 coils/cm or more and hypocoiling as 0.1 coils/cm or less.[3] The coiling of the umbilical cord is clearly present by 7 to 10 weeks' gestation; coiling may begin as early as 28 to 35 days postfertilization. It has been demonstrated that coiling of the umbilical cord may increase only slightly into the third trimester.[39–41]

Abnormalities in cord coiling have been found to be associated with adverse pregnancy outcomes, including stillbirth. Cord hypercoiling occurs in up to 20% of pregnancies; however, hypercoiled umbilical cords infer an increased risk for pregnancy complications, including fetal demise (Figure 2). This is likely due to the increased risk for fetal vascular flow obstruction, including fetal thrombi, avascular villi, and fetal thrombotic vasculopathy. In 2007, de Laat et al reviewed 565 placentas that had an indication for examination.[41] Among these cases, hypercoiling was

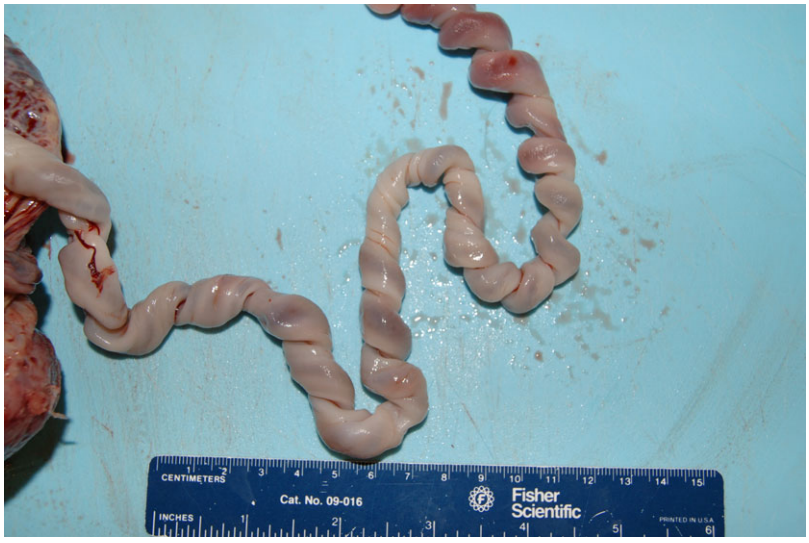

Figure 2. Hypercoiling Identified in a 37-week Stillbirth

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associated with fetal death (OR, 3.74; 95% CI, 1.89-7.40), umbilical arterial pH less than 7.05 (OR, 3.63; 95% CI, 1.44-9.17), thrombosis in fetal placental vessels (OR, 2.64; 95% CI, 1.37-5.06), iatrogenic preterm birth (OR, 1.91; 95% CI, 1.04-3.49), chronic fetal hypoxia (OR, 1.82; CI, 1.09-3.05), and fetal aneuploidy or congenital anomalies (OR, 1.79; 95% CI, 1.01-3.16). Cord hypocoiling can also be associated with increased risk for poor pregnancy outcomes. In the same study by de Laat et al, undercoiled umbilical cords were associated with a higher frequency of chorioamnionitis (OR, 1.77; 95% CI, 1.09-2.88), aneuploidy or congenital anomalies (OR, 1.78; 95% CI, 1.08-2.95), low Apgar score ($P = .03$), and fetal death (OR, 4.09; 95% CI, 2.22-7.55).[41] The postulated explanation for increased risk of chorioamnionitis with undercoiled umbilical cords is the presence of a less turgid, or weak, stroma. A weak umbilical cord stroma may be associated with a weaker chorionic and amniotic membrane that allows the penetration of ascending infection.[41]

The direction of coiling, leftward (counterclockwise) or rightward (clockwise), can also be observed. To determine the direction of coiling, the umbilical cord is held taut and the upward direction of the twist observed.[31] Right-handed cord coiling is less common than left-handed cord coiling in the general population; it is proposed that the umbilical cord naturally favors left-handed coiling because the right umbilical artery is larger than the left (this size discrepancy creates a left-handed rotational torque). Thus, right-handed coiling may indicate a developmental abnormality. In a study of 318 hypercoiled placentas, Ernst et al found that right-handed cord coiling was associated with the highest incidence of fetal vascular flow obstruction and stillbirth.[40] In addition, cords demonstrating the greatest constriction of cord diameter between coils (segmented and linked patterns) had the greatest association with the poorest pregnancy outcomes.[40]

Continuity of the Umbilical Cord

Knots of the umbilical cord include *false* and *true* knots. A *false* knot occurs secondary to kinking of the vessels and is identified as a varicosity. A *false* knot is generally of no clinical significance. A *true* knot, however, is associated with low 1-minute (OR, 1.67; 95% CI, 1.10-2.54) and 5-minute (OR, 2.00; 95% CI, 1.13-3.54) Apgar scores, small for gestational age (OR, 3.17; 95% CI, 2.18-4.62), neonatal intensive care unit admission (OR, 1.58; 95% CI, 1.07-2.33), and fetal death (OR, 8.08; 95% CI, 1.50-43.57).[42] Fetal death results from compression of the fetal circulation.[23] True knots are identified in 1.2% of all pregnancies (Figure 3) and have been attributed to fetal movement.[42] Risk factors have been identified as advanced maternal age; multiparity; and pregnancies characterized by a male fetus, monoamnionic twins, polyhydramnios, and a long umbilical cord. Attributing fetal death to an umbilical cord knot is done cautiously because most occurrences of true knots are observed in live births.[7]

Umbilical cord *torsion* also results from fetal movements and is an accentuation of normal cord coiling. Marked torsion can result in vasculature compromise, including congestion, edema, and thrombus formation.[3] Umbilical cord *strictures* occur at sites deficient in Wharton jelly and similarly result in vasculature compromise.[3] Cord entanglements, nuchal loops, and body loops are common and occur in 30% of pregnancies.[7] Looping of the cord is associated with an excessively long cord. At the time of birth, such entanglements are documented. A groove on the fetal skin can be observed in cases of severe entanglement.

Umbilical cord inflammation (*funisitis*) is associated with an infection of the amniotic fluid. The influx of inflammatory cells into the umbilical cord results in umbilical vein angiitis. Inflammation of the umbilical cord vasculature has been theorized to result in vasoconstriction and the sequela of fetal ischemia.[23] On examination of the umbilical cord, swelling, calcifications, and exudate may be present.[43] The examiner may also appreciate a foul odor. Necrotizing funisitis is a distinct finding and is associated with infections such as syphilis and herpes, premature rupture of membranes, fetal growth restriction, and fetal demise.[23] The umbilical cord in necrotizing funisitis has been described as resembling a barber pole.[23] This unique appearance of the umbilical cord

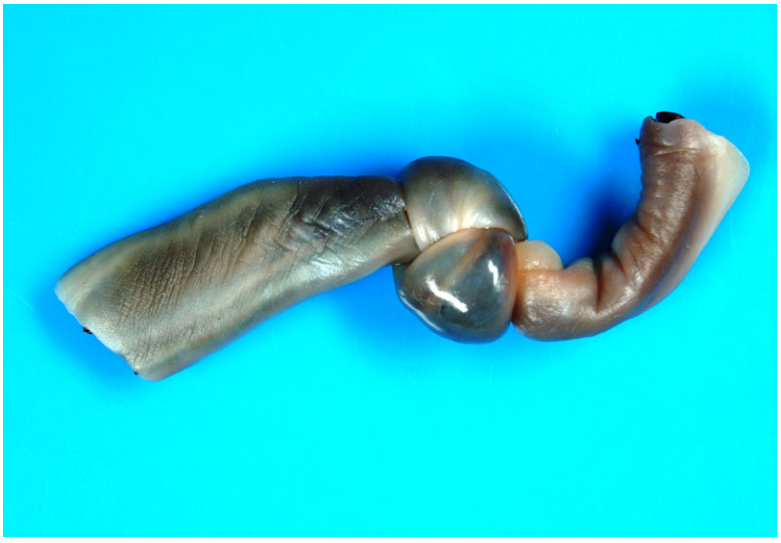

Figure 3. Tight True Knot

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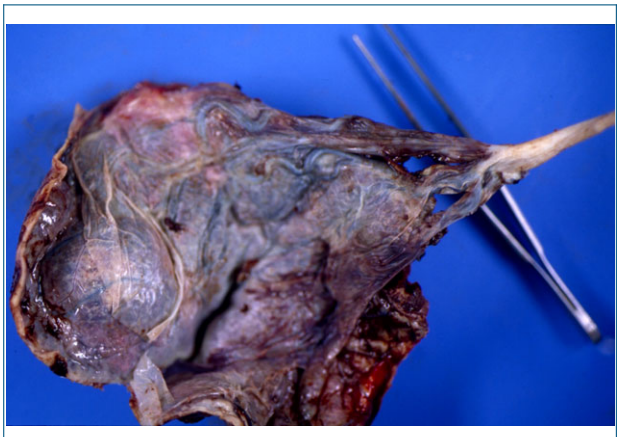

Figure 4. Velamentous Umbilical Cord Insertion

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is attributed to perivascular concentric rings of inflammatory cells, with resultant necrosis and calcium deposition.[23] Necrotizing funisitis can result in umbilical cord rupture due to increased tissue friability.

Insertion Site

Normal umbilical cord insertion is at or near the center of the fetal surface of the placenta. Abnormal insertion increases the risk of umbilical cord compromise. In velamentous insertion, the umbilical vessels separate in the membranes at a distance from the placental margin (Figure 4). The umbilical cord is left unsupported by Wharton's jelly, which places the fetal vessels at risk for obstruction or damage. The risk of these events is increased as the distance between the cord insertion and disc margin and length of the membranous vessels increases.[3] Velamentous cord insertion is identified in 1% of singleton pregnancies, 9% of twin pregnancies, and 1% of stillbirths.[3] It is more common in multifetal gestations, abnormal placental lobation, and in those with a single umbilical artery.[23] An increased risk of umbilical cord occlusion is observed with greater distance between cord insertion and disc margin, as well as increased length of the vessels.

Furcate (forked) insertion is a rare abnormality in which the umbilical vessels separate prior to their insertion into the placental disc, distinct from velamentous insertion in which the umbilical vessels insert into the membranes. Without the protection of Wharton's jelly, the fetal vessels are at risk for compression and trauma, and fetal death can ensue.[3]

In marginal (Battledore) insertion, the umbilical vessels insert at the edge of the placental disc. Marginal insertion is present in 7% of pregnancies.[3] In this type of insertion, the umbilical vessels are at increased risk for rupture during amniotomy or labor, and twisting resulting in vascular rupture or occlusion.

MULTIPLE GESTATIONS

As compared to singletons, women with a multiple gestation have a 4-fold greater incidence of stillbirth.[9] Although similar etiologies are present, multiple gestations have several unique causes such as TTTS and cord entanglement.

After the birth of a multiple gestation, the number of placentas and amniotic membranes are documented. Chorionicity is determined by assessing the thickness of the dividing membranes and the attachment of the dividing membranes to the placental disc.[2] There are 3 types of twin placentation: 1) diamniotic-dichorionic, 2) diamniotic-monochorionic, and 3) monoamniotic-monochorionic. In the diamniotic-dichorionic gestation, the 2 placentas may be separate or fused. The monoamniotic-monochorionic gestation (1/10,000 pregnancies) has the greatest risk for stillbirth, with a perinatal mortality rate of 33% to 70%.[23] Fetal demise in these pregnancies is associated with cord entanglement, cord prolapse, and fetal malformations. Approximately 20% of twins will have a diamniotic-monochorionic structure.[24]

Table 2. Placental Examination Checklist

Placental Anatomy
Placental Disc
Size
Weight (kg)
Diameter (cm)
Structure
Intact (yes/no)
Accessory lobes (yes/no)
Lesions
Maternal surface (calcifications, hematoma, infarct)
Fetal surface (hemangioma)
Amnion
Color
Lesions (amnion nodosa, bands)
Umbilical Cord
Structure
Number of vessels
Length (cm)
Coiling (normal, hypo-, hyper-)
Continuity (knots, torsion)
Insertion site (central, velamentous, marginal, furcate)
Multiple Gestation
Chorionicity
Amnionicity

TTTS occurs in 15% of diamniotic-monochorionic gestations and results from an unbalanced placental artery-to-vein anastomosis.[3,23] The vascular anastomosis is comprised of a donor twin's artery supplying a cotyledon while the recipient twin's vein drains the cotyledon. The artery-to-vein anastomosis results in an efflux of blood from the donor twin to the recipient twin, causing discordant growth, oligohydramnios in the donor twin, and polyhydramnios in the recipient twin.[24] Fetal mortality in TTTS is attributed to fetal anemia in the donor twin and fetal hydrops in the recipient twin.[23] On examination of the placenta, the arterial-to-vein anastomosis can be identified. Arteries always cross over veins; therefore, these 2 vessels can be distinguished from one another.[24]

At the time of birth of a twin gestation, the umbilical cord of twin A and B are differentiated. Typically, one clamp on the umbilical cord of A and 2 clamps on the umbilical cord of B will differentiate the tissues related to each fetus.

PATHOLOGIC EXAMINATION

In accordance with the 1997 College of American Pathologists guidelines,[22] all placentas from a stillbirth should undergo pathologic examination. After completion of the gross placental examination, normal and abnormal findings are recorded in the woman's chart. Table 2 provides a checklist for the gross placental examination and can serve as a template for documentation.

Prior to submitting the placenta to pathology, dissecting a wedge of the placenta for genetic testing should be considered. Chromosomal microarray is recommended in place of standard karyotype analysis in all cases of stillbirth.[44] The detection rate for genetic abnormalities increases by 24% when microarray analysis is performed, which is attributed to both its higher resolution and ability to perform analysis on uncultured cells (nondividing cells). Karyotype can only detect deletions or duplications 3 to 10 megabases in size, whereas a microarray can detect abnormalities as small as a single nucleotide change. Because karyotyping requires cell culture and 50% of samples from a fetal demise fail to culture, the ability to analyze the specimen directly with chromosomal microarray is advantageous. A placental block that includes the chorionic plate is obtained below the cord insertion site and placed in sterile tissue culture medium of lactated ringers at room temperature.

The pathologist should be provided with the maternal medical and obstetric history, estimated time/date of fetal death and birth, fetal weight and gestational age, and any notable fetal abnormalities.[3] The placenta can be placed in a 1- to 2-L container with 100 to 200 mL of normal saline. Fixation should not be performed.[23] Placing the placenta in formalin changes its consistency and prevents identification of the pathologic color changes. If immediate transfer to the pathology department is not feasible, the placenta can be stored at 4°C.[3]

STILLBIRTH ASSESSMENT PROGRAMS

Several stillbirth assessment programs have been established in an effort to reduce the incidence of stillbirth in the United States. The Wisconsin Stillbirth Service Program (WiSSP) was started in 1983 as a collaborative community-based program that uses an algorithm to investigate the cause of fetal death.[45] The goal of WiSSP is to provide families and medical providers with a thorough evaluation of the stillbirth, identify plausible cause(s) of death, and provide recommendations for the management of future pregnancies. The service is free of charge.

Between 2004 and 2010, WiSSP reviewed 416 cases of stillbirth using a uniform protocol, which included review of maternal and family histories, maternal laboratory evaluation, fetal dysmorphologic examination, fetal autopsy, fetal karyotype, and placental assessment. A cause was identified in 70% of cases.[46]

The WiSSP emphasizes that assessment programs should not focus on identifying a single cause of death. Although a single abnormality may initially be identified as the cause of death, a thorough assessment is recommended to identify all contributing factors. In a review of 416 stillbirth cases, over half (53.4%) had 2 different abnormalities identified, whereas 14.9% had 3 significant findings.[46] The counseling of women and management of future pregnancies is dependent on identifying all potential contributors.

Modeled after the WiSSP program, the Kate Cares program at Indiana University School of Medicine, Indianapolis, was established in 2003. In the Kate Cares program, multiple

subspecialties including maternal–fetal medicine, neonatology, genetics, and pathology contribute to a multidisciplinary evaluation of women who have experienced a stillbirth. The primary goal of the program is to perform an extensive review of the woman's medical and pregnancy history, assess for possible causes of the stillbirth, and provide recommendations for future pregnancies. Referring physicians are provided with a summary letter of the findings and recommendations of the Kate Cares review committee. The committee's review is at no cost to the family. This regional program serves in a similar capacity as the WiSSP program by providing a formal evaluation of the potential etiologic factors for an observed stillbirth.

CONCLUSION

A stillborn fetus is an unsuccessful end to gestation and is an undesired outcome for women and their families. The search for causative factors can often be challenging because it entails a review of risk factors throughout the pregnancy. Maternity care providers and birth attendants have a unique opportunity to gather information on the stillbirth by completing a thorough evaluation of the placenta and associated tissues. In this article, we have outlined an approach to the systematic evaluation of the stillborn placenta with a focus on macroscopic features that can be observed on gross examination. Information obtained from evaluation of the placenta can be integrated into a broader review of a woman's pregnancy course. Identifying the cause of stillbirth can help families searching to understand why their pregnancy was not successful. For health care providers, knowledge of the etiology of a stillbirth can facilitate counseling by providing a recurrence risk for future pregnancies and guide interventions such as lifestyle modifications or changes in the woman's medical management.[8] Alternatively, appropriate counseling may allow couples to avoid unnecessary testing in future pregnancies.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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