Pathological examination of the placenta: *Raison d'être*, clinical relevance and medicolegal utility

Chang K T E

ABSTRACT

Formal pathological examination of the placenta provides valuable information to the obstetrician, neonatologist, paediatrician and family. This article aims to provide the clinician with an overview of the significance of placental examination in relation to common or important pathological processes, and the utility of information obtained therein in explaining adverse outcomes, management of subsequent pregnancies, and assessment of newborn risk for the development of short- or long-term sequelae. General guidelines for placental examination, and logistical and practical issues are also discussed. Finally, the role of the placenta in the defence of obstetricians and other healthcare workers in cases of poor neonatal outcome is described.

Keywords: medicolegal, placenta, placental pathological examination, poor neonatal outcome

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INTRODUCTION

The placenta is a unique gestational organ which functions as the fount upon which the developing foetus derives its nutritional sustenance and obtains its metabolic and immunological requirements. Its strategic location at the foetomaternal interface provides a record of pregnancy in which the cumulative effects of pregnancy-related events and changes reflecting the intrauterine environment can be scrutinised in what is effectively a whole organ biopsy.

Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899

Chang KTE, MBChB, FRCPath
Consultant and Head, Children's Pathology

Correspondence to:
Dr Kenneth TE Chang
Tel: (65) 6394 1363
Fax: (65) 6394 1372
Email: kenneth.chang.te@kkh.com.sg

CLINICAL BENEFITS AND OUTCOMES

Although dissenting opinions have been propounded in the past,[1] the positive clinical value of placental examination is currently well accepted.[2] The benefits of placental examination include the following:[3]

(1) Provision of an audit of antenatal clinical judgment and management;
(2) Identification of aetiologies and pathological processes contributing to or causing an adverse pregnancy outcome;
(3) Improved management of subsequent pregnancies by the identification of conditions known to have recurrence risks or which may be either treatable or preventable;
(4) Identification of a pathological condition requiring timely clinical intervention;
(5) Understanding of antenatal and intrapartum events that contribute to long-term neurodevelopmental sequelae, with early identification of such changes making possible early interventions and improvement in long-term outcome;
(6) Assessment of factors contributing to poor outcome as a factual basis for resolving medicolegal issues.

The multidisciplinary team approach is well established in oncology.[4] A similar model for perinatal medicine is appropriate,[5] and may involve obstetricians, neonatologists, ultrasonographers, obstetrical anaesthetists, clinical geneticists, paediatric surgeons and paediatric pathologists. This may serve both as a working conference to review and discuss current case issues, and as a teaching conference. Cases of stillbirths and adverse neonatal outcome may be discussed at this conference with appropriate placental and autopsy pathology input.

INDICATIONS FOR FORMAL PATHOLOGICAL EXAMINATION

All placentas should be examined grossly, at least. This may be performed by the healthcare providers present at the time of birth and can be accomplished with a basic knowledge of placental anatomy and pathology, and an understanding of the abnormalities and variations that affect the placenta.[6] While some advocate formal pathological examination of all placentas, few institutions have sufficient manpower or financial resources to accomplish a task of such Herculean proportions.[7] Since the vast majority of pregnancies, and hence newborns and placentas are normal, it follows that only a subset of placentas requires submission to the pathology department for formal gross and histological examination. The Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists has

Table I. Indications for placental examination.[3]

Maternal indications
Systemic disorders (e.g. diabetes mellitus, hypertensive disorders, collagen vascular disease)
Premature delivery ≤ 34 weeks gestation
Peripartum fever and/or infection
Unexplained third-trimester bleeding or excessive bleeding
Clinical concern for infection, e.g. HIV, TORCH infections
Severe oligohydramnios
Unexplained/recurrent pregnancy complication (e.g. intrauterine growth retardation, stillbirth, spontaneous abortion, premature birth)
Invasive procedures with suspected placental injury
Placental abruption
Non-elective pregnancy termination
Thick and/or viscid meconium
Foetal indications
Admission or transfer to other than a Level I nursery
Stillbirth or perinatal death
Compromised clinical condition
Hydrops foetalis
Birthweight less than the tenth percentile
Seizures
Infection or sepsis
Major congenital anomalies, dysmorphic phenotype or abnormal karyotype
Discordant twin growth > 20% difference
Multiple gestation with same-gender infants and fused placentas
Placental indications
Physical abnormality (e.g. infarct, mass, vascular thrombosis, retroplacental haematoma, amnion nodosum, abnormal colouration or opacification, malodour)
Small or large placental size or weight for gestational age
Umbilical cord lesions (e.g. thrombosis, torsion, true knot, single artery, absence of Wharton's jelly)
Total umbilical cord length < 32 cm at term

drawn up a set of indications for submission of placentas for formal pathological examination (Table I),[3] which individual institutions may adapt to meet the needs of the patient populations they serve. A published audit on conformity to guidelines for submission of placentas for pathological examination revealed a low level of conformity,[8] and periodic review or audit on conformity to institutional guidelines may optimise submission rates.

Placentas submitted to the pathology laboratory for examination should be accompanied by a specimen requisition form containing clinical information. Such information should include gravidity and parity, obstetric history, obstetric estimate of gestational age, route of delivery, foetal birth weight, gender, Apgar scores, maternal and foetal complications of pregnancy, labour, delivery, and total umbilical cord length. Alternatively, the birth record may be submitted if such information is contained therein. A dedicated specimen requisition form can be utilised to facilitate the provision of such information to the pathologist. The indication(s) for which the placenta is being submitted should be stated. The importance of providing the above clinical information cannot be overemphasised, as an absence of clinical data hampers meaningful pathological evaluation and correlation of clinical findings with gross and histological findings.[9]

PLACENTAL HANDLING AND TRANSPORT

Fresh placental tissue is required for bacterial and viral cultures, cytogenetic studies and metabolic studies. Tissue for electron microscopy may be obtained from either fresh or formalin-fixed tissue. Following tissue procurement for the above purposes, individual institutional guidelines can indicate whether the placenta should thereafter be placed in fixative, since some pathologists prefer to examine the placenta fresh, while others prefer examination following fixation. If a delay is anticipated between delivery and receipt at the pathology department, e.g. because of transportation, refrigeration is an alternative to fixation. Placentas should not be frozen since this introduces artifacts which hamper histological evaluation. Refrigerated placentas may be stored in individual, labelled, water-resistent containers, e.g. plastic or styrofoam containers.

All placentas, like other tissues received in the pathology laboratory, should be considered potentially infectious, and should be handled in accordance to universal precautions. It is ideal for all placentas not

Table II. Nomenclature of amniotic fluid infection.[17]

Maternal inflammatory response	
Stage 1 (Early)	Acute subchorionitis or chorionitis
Stage 2 (Intermediate)	Acute chorioamnionitis
Stage 3 (Advanced)	Necrotising chorioamnionitis
Grade 1 (Mild–moderate)	
Grade 2 (Severe)	Severe acute chorioamnionitis or with subchorionic microabscesses
Other	Chronic (or subacute) chorioamnionitis
Foetal inflammatory response	
Stage 1 (Early)	Chorionic vasculitis or umbilical phlebitis
Stage 2 (Intermediate)	Umbilical arteritis or umbilical panvasculitis
Stage 3 (Advanced)	(Subacute) necrotising funisitis or concentric umbilical perivasculitis
Grade 1 (Mild–moderate)	
Grade 2 (Severe)	Severe foetal inflammatory response or with intense chorionic (umbilical) vasculitis
Other	Associated foetal vessel thrombi
Other specific features	
Peripheral funisitis	
Acute villitis	
Acute intervillositis with intervillous abscesses	
Decidual plasma cells	

requiring formal pathological examination to be stored refrigerated for at least a week in the event of a change in the clinical status of the newborn, whereupon the placenta can be retrieved for formal examination.

PATHOLOGICAL EVALUATION AND REPORTING

The oft-cited scenario in which obstetrical caregivers submit a placenta for pathological examination in a case of unexpected poor outcome, and receive a report many days or weeks later, with a diagnosis of "placenta confirmed", which gives rise to a vicious cycle effect and removes all impetus to continue seeking pathological consultation. This should hopefully be eradicated through the development of interest and expertise on the part of the pathologist, and an understanding of the utility and clinical significance of pathological examination on the part of the clinician. A previous study revealed that general surgical pathologists have a higher rate of underdiagnosis of placental lesions compared to paediatric pathologists.[10] Such a phenomenon is not exclusive to the realm of placental pathology, and underlines the fact that the reporting pathologist should be adequately trained and sufficiently experienced in placental pathology.

An audit was performed on the quality of placental reports, which showed that different aspects of gross and histological examinations and commentaries on abnormalities in relation to clinical indications were inconsistently reported. It was suggested that the use of templates and checklists for the reporting of placentas may help improve the completeness and overall standard of reporting.[11] It is debatable as to whether the placental pathology report should be filed with the case notes of the mother or the baby. Traditionally, the report is filed with the mother's case notes. However, this means that neonatologists or paediatricians caring for a newborn would be unaware of the information reported therein. I suggest that copies of the placental pathology report be filed in both the mother's and newborn's case notes.

MAJOR PATHOLOGICAL CATEGORIES

Acute chorioamnionitis

Acute chorioamnionitis is defined histologically by the presence of acute inflammatory cells within the foetal membranes. It indicates infection in the amniotic cavity due to an ascending bacterial infection. There is poor correlation of histological acute chorioamnionitis with "clinical" acute chorioamnionitis, as defined by fever, leucocytosis, uterine tenderness, or maternal or foetal tachycardia. Women with histological acute chorioamnionitis may not have clinical manifestations of clinical chorioamnionitis.[12] Conversely, only a proportion of women with clinical acute chorioamnionitis show histological evidence of acute chorioamnionitis.[13] At present, histological chorioamnionitis has been shown to be both sensitive and specific for infection and is the gold standard against which other clinical predictors of infection are measured.[14-16]

The mother and baby both contribute to the inflammatory response in amniotic infection. The maternal response begins with the emigration of neutrophils from decidual vessels and intervillous spaces. The neutrophils then spread through the chorion and amnion in response to chemotactic factors in the amniotic fluid. The foetal response occurs later than the maternal response, but only if the infant remains alive and is older than 20

weeks in gestational age. It consists of vasculitis within the umbilical cord affecting the umbilical vein, then the arteries, and the chorionic plate surface vessels.

A recent proposal to grade and stage amniotic infections has been proposed[17] (Table II), but acceptance of the need and clinical significance of grading and staging is by no means universal. Although grading and staging do have some significance in relation to neonatal outcome, the most important features of ascending infection are the identity of the infectious agent and whether there is a foetal response, e.g. *Trichomonas* spp. often elicits a heavy and dense neutrophilic infiltrate, yet has little effect on neonatal wellbeing. Conversely, Group B streptococcal infection is one of the most virulent perinatal infections, yet intraamniotic infection and neonatal sepsis may occur without identifiable histological chorioamnionitis.[18]

Nonetheless, specific histological findings have been shown to have prognostic significance in relation to foetal outcome. Necrotising chorioamnionitis is a late complication of amniotic inflammation, and is associated with an increased risk of perinatal death and preterm delivery,[19] and should be specified by the pathologist in the pathology report. Necrotising chorioamnionitis is also associated with preterm labour, premature rupture of membranes, and decreased gestational age in very low birthweight infants.[20] Necrotising funisitis is a severe pattern of umbilical cord inflammation characterised by yellow-white calcific rings around the cord vessels. It is rare, but has a high association with significant foetal and neonatal morbidity and mortality.[21]

From a practical point of view, there are important questions that require answers when a potentially inflammed placenta is submitted for pathological examination.[22] First, is fever, abdominal tenderness or maternal leucocytosis due to chorioamnionitis or some other condition, e.g. cervical incompetence, maternal vascular disease, chronic placental abruption? And are symptoms and signs in the newborn, such as growth retardation, abnormal neurological status, cytopenia and organomegaly, explained by infection, or should some other cause, such as metabolic or congenital heart disease, need to be pursued? Second, certain infectious organisms, such as *Candida albicans, Listeria monocytogenes* and *Treponema pallidum,* are treatable; is the cause of infection due to one of these organisms? Third, what are the long-term consequences for the mother and foetus in terms of recurrence in future pregnancies and risk of neurological impairment?

Table III. Grading of chronic villitis (after Redline).[27]

Low grade	Involvement of less than ten chorionic villi
Focal	Only one slide involved
Multifocal	More than one slide involved
High grade	Involvement of more than ten chorionic villi per focus
Patchy	≤ 5% of chorionic villi involved
Diffuse	> 5% of chorionic villi involved

Chronic villitis

Chronic villitis is defined histologically as an infiltrate of lymphocytes and histiocytes affecting the chorionic villi. It is a relatively common process which can be identified in up to 15% of term placentas. Chronic villitis may be infectious (approximately 10% of all cases of chronic villitis) in which there is a specific aetiologic agent, or it may be nonspecific, where no infectious cause is identified by clinical, morphological, serological or microbiological investigations. Infectious causes of chronic villitis include the TORCH (toxoplasma, rubella, cytomegalovirus and Herpes simplex) infections. These may recur in a minority of cases, and are associated with perinatal mortality. Infectious causes which are evident on histological examination include cytomegalovirus, syphilis, toxoplasmosis and Herpes simplex virus. The chronic inflammatory infiltrates of infectious chronic villitides include plasma cells, which are an important clue to the evaluating pathologist that the chronic villitis is infectious in origin.

In contrast, nonspecific lymphohistiocytic chronic villitis, termed villitis of unknown aetiology (VUE), is characterised histologically by an infiltrate composed of lymphocytes and histiocytes,[23] and lacking plasma cells. The majority of lymphocytes are maternally-derived CD8-positive cytotoxic T lymphocytes,[24] indicating that VUE is a host-derived inflammatory response occurring within a donor allograft tissue. The non-lymphoid component of the infiltrate consists of resident foetal villous macrophages (Hofbauer cells) which function as antigen-presenting cells, and perivillous monocyte-macrophages of maternal origin.[25] Foetal Hofbauer cells have been shown to proliferate in VUE and become activated as evidenced by the up-regulation of class II major histocompatibility complex antigen expression.[26] Epithelioid histiocytes and multinucleate giant cells may be identified histologically, but their presence in otherwise typical VUE should not raise suspicion of mycobacterial or fungal infections, which do not cause chronic villitis of this pattern.

VUE may be graded using the grading system of Redline[27] (Table III). VUE has significant clinical associations. Studies have shown VUE to be associated with intrauterine growth restriction (IUGR),[28,29] and the frequency of IUGR with VUE appears to be proportional

to the extent of villous involvement. High-grade VUE is also associated with an increased risk of adverse foetal neurological outcome.[30] In addition, high-grade and diffuse VUE is commonly associated with increased perivillous fibrinoid deposition, a process that increases the risks of IUGR, prematurity and stillbirth.[27] VUE recurs,[31] and recurrent VUE is associated with significant perinatal mortality.[32] Administration of aspirin and corticosteroids has been suggested to manage subsequent pregnancies, but further clinical evaluation of this and other therapeutic regimens is warranted.[33]

Foetal vascular obstructive lesions and foetal thrombotic vasculopathy

The placenta is a richly vascular organ where the two separate circulatory systems of foetus and mother interface. Thrombotic or occlusive lesions may occur within the foetal circulation with potentially serious consequences to the foetus. Pathophysiologically, foetal vascular obstructive lesions are the result of Virchow's triad of stasis, hypercoagulability and vascular damage within the foetal circulation of the placenta.[34] Stasis within the foetal circulation may be the result of a compromise of blood flow through the umbilical cord resulting from prolonged umbilical cord compression, cord entanglement, abnormal insertion, or abnormal length or coiling, intrauterine foetal heart failure (hydrops foetalis), or polycythaemia.[35] Hypercoagulability may result from poorly-controlled maternal diabetes mellitus, autoimmune conditions (e.g. antiplatelet antibodies or antiphospholipid syndrome), or maternal or foetal thrombophilias. Foetal vascular injury may result from the foetal inflammatory response to severe chorioamnionitis, meconium toxicity or haemorrhagic endovasculitis. Foetal thrombophilia alone does not correlate with an increase in placental foetal vascular pathology,[36] and likely acts synergistically with other risk factors.

The morphological lesions seen in foetal vascular obstruction are varied.[37] Gross manifestations are rare, but should be carefully looked for by the examining pathologist. These include thrombi within the umbilical cord vasculature or surface chorionic vessels. Such gross findings require histological confirmation. Histological manifestations include intimal fibrin cushions[38] or fibromuscular sclerosis affecting large foetal vessels, haemorrhagic endovasculitis (villous stromal-vascular karyorrhexis) and avascular chorionic villi.[39] There is prognostic importance in distinguishing the severity of involvement with foetal vascular obstructive lesions.[30,31,39] The Fetal Vascular Obstruction Nosology Committee, formed under the auspices of the Society for Pediatric Pathology, therefore, makes the distinction between a less severe subgroup designated "changes consistent with chronic foetal vascular obstruction" and a more severe subgroup of "foetal thrombotic vasculopathy".[37]

The foetal consequences of foetal vascular obstruction depend on the distribution and number of the thrombi. If multiple large chorionic veins or the umbilical vein is involved, the consequences include intrauterine foetal death, perinatal asphyxia and hydrops foetalis. Foetal systemic thromboembolism is a potential complication of thrombi in large chorionic surface veins. Other clinical associations of foetal thrombotic vasculopathy include intrauterine growth restriction, foetal seizures, amputation necroses of foetal limbs, neonatal stroke, cerebral palsy and poor long-term neurological outcome.

Maternal vascular malperfusion and placental infarction

Oxygenation of the placenta, and hence of the foetal circulation, depends on adequate perfusion of the maternal vascular (i.e. intervillous) space by oxygenated maternal blood via maternal uterine and decidual arteries. During the course of pregnancy, the maternal arteries undergo physiological conversion, a process by which trophoblastic invasion of the uteroplacental vessels convert relatively small-calibre muscular arteries to large-calibre and low-resistance vascular channels.[40] Abnormalities of this process results in decidual vasculopathy and a spectrum of pathological features affecting the maternal vasculature, including acute atherosis, mural hypertrophy of the membrane arterioles and muscularised basal plate arteries.[41] Villous malperfusion results in accelerated villous maturation. This is a process in which histological features of distal villous hypoplasia and Tenney-Parker changes impart to the placenta a histological appearance of development and maturation which is advanced for its actual gestational age. In addition, such placentas are often small for the gestational age[42] and have an increased foetal-placental weight ratio.

Complete cessation of maternal vascular perfusion to a region of the placenta results in infarction. Small infarcts at term may not have clinical significance. Large or multiple small infarcts involving a substantial proportion of the placenta, or infarcts in premature placentas are markers for significant maternal vascular disease, especially hypertension. They are associated with significant risk for adverse pregnancy outcome. Features of decidual vasculopathy, accelerated villous maturation and placental infarction are seen in pregnancies affected by preeclampsia and gestational hypertension, lupus erythematosus, and in women with lupus anticoagulant

and antiphospholipid antibodies. The presence of antiphospholipid antibody is associated with recurrent abortions.[43] Maternal vascular underperfusion is an important cause of foetal growth restriction, preterm rupture of membranes and preterm labour.[44-47]

Placental haematomas and thrombi

Placental haematoma or thrombi formation may occur at various anatomical localities within the placenta, and include retroplacental haematomas, marginal haematomas, intervillous thrombi, subchorionic thrombi, and subamniotic haematomas.

Retroplacental haematomas are the morphological substrate for the clinical syndrome of abruption placentae. In the classical case, the pathologist finds a large laminated blood clot adherent to the maternal surface of the placenta, compressing the overlying placental parenchyma. Such findings require hours or days to develop. A more acutely-developing retroplacental haematoma may not be accompanied by such changes, and may be non-adherent to the placenta. In such situations, the pathologist is reliant on information provided by the clinician. Morphological clues to the occurrence of a significant acute retroplacental haematoma include a fixed depression in the maternal surface, histological findings of decidua basalis haemorrhage with necrosis and inflammation, adjacent intravillous haemorrhage, and in some situations, early villous infarction. The causes of retroplacental haemorrhage are varied, but in a significant proportion, are related to abnormalities of the vascular bed arteries. Retroplacental haematomas occupying more than a third of the maternal floor of the placenta are associated with significant foetal morbidity and mortality.

Marginal haematomas are crescent-shaped clots located at the margin of the placental disc. Small marginal haematomas are not uncommon. Their significance is in relation to antepartum per vaginal bleeding,[48] and as a possible nidus for the development of placental infection.

Intervillous thrombi are blood clots occurring within the placental parenchyma which result in displacement and compression, and sometimes infarction, of the surrounding chorionic villi. They are formed of a mixture of foetal and maternal blood. The significance of intervillous thrombi is as an indicator of foetal bleeding into the intervillous space and hence into the maternal circulation.[49] Small intervillous thrombi are not uncommon lesions, and often have no effect on placental function or foetal well-being. Massive intervillous thrombi are frequently associated with poor perinatal outcome. In the event of significant neonatal anaemia, stillbirth or other adverse neonatal outcome, the Kleihaur-Betke test may be helpful in assessing the presence, chronicity and severity of foetal to maternal haemorrhage.

Subchorionic haematomas form in small quantities physiologically as a result of backwards deflection and eddying of maternal blood in this locality.[50] Massive subchorionic haematomas involving more than 50% of the placental disc are associated with poor reproductive outcome, including preterm delivery, abortions, intrauterine foetal growth restriction and intrauterine foetal death. There is an association with maternal circulatory disorders including maternal diabetes mellitus, cardiac disease, hypertension and thrombophilias.[51] The Breus' mole is an overlapping entity – a massive subchorionic haematoma which is diffusely nodular and which forms blood-filled protrusions when viewed from the foetal aspect of the placenta.[52] It is associated with circumvallation, neonatal demise, monosomy X, and maternal diseases such as diabetes mellitus and hypertension.

Subamniotic haemorrhages or haematomas are free-lying collections of blood located between the amnion and chorion on the foetal plate of the placenta. They arise due to trauma to the surface vessels as a result of traction on the umbilical cord during delivery, and are common in specimens from caesarean deliveries. They are usually of no clinical significance.

Massive perivillous fibrinoid deposition and maternal floor infarction

Massive perivillous fibrinoid deposition (MPFD) and maternal floor infarction (MFI) are related entities characterised by excessive deposition of fibrinoid in the placental parenchyma. The pregnant patient with MPFD/MFI is typically clinically normal; a drop-off of foetal growth or decreased foetal movements in the late second or third trimesters may be the only indication of underlying pathology. Elevation in maternal serum alpha foetoprotein may be detected from the second trimester, with significant elevation in major basic protein levels in some patients.

In MPFD, the pattern of fibrinoid deposition is diffuse, while in MFI, the fibrinoid is laid down along the maternal floor of the placenta. Semi-quantitative histological definitions for MPFD and MFI have been proposed by Katzman and Genest to improve the reproducibility of diagnosis[53] (Table IV). The cause remains unknown, but suggested aetiologies include autoimmune disease,[54] activated protein C resistance,[55] latent herpes infection,[56] and a toxic insult mediated by pregnancy-associated major basic protein.[57] The process may represent a final common pathway from a variety of chorionic villus injuries in association with stasis of the intervillous circulation.[58]

Table IV. Semi-quantitative definitions for maternal floor infarction/massive perivillous fibrinoid deposition.[53]

Classic MFI	Basal villi of the entire maternal floor encased by perivillous fibrinoid of ≥ 3 mm thickness on at least one slide.
Transmural MPFD	Perivillous fibrinoid material extending from the maternal surface to foetal surface, encasing ≥ 50% of the villi on at least one slide.
Borderline MPFD	25%–50% villi on at least one slide encased by perivillous fibrinoid material in a transmural, or nearly transmural, distribution.

MFI: maternal floor infarction; MPFD: massive perivillous fibrinoid deposition

The clinical importance of these lesions relates to the associated poor outcome for the foetus and for the high risk of recurrence in future pregnancies. Although the condition is rare, with an incidence of between 0.09% and 0.5%.[58,59] stillbirth is reported to occur in up to 50% of affected pregnancies. There is also increased frequency of intrauterine growth restriction, and increased incidence of preterm delivery.[60] The disorder can occur in the first and second trimesters,[53] when it is associated with recurrent miscarriages. There is also a significant recurrence risk for the mother estimated to be at least about 20%.[60,61]

A pathological diagnosis of MPFD/MFI mandates intervention by the clinician in subsequent pregnancies. Ultrasonographical criteria have been defined and allow prenatal diagnosis and monitoring.[62] Successful intervention strategies have included aspirin and heparin,[63] presumably related to prevention of platelet aggregation and thrombosis. Although early miscarriages in these patients may be reduced by therapy, late prenatal complications may still develop, and close continued monitoring and treatment are necessary.[64]

Meconium staining

Meconium is the normally-sterile content of the foetal lower intestinal tract, comprising bile pigment, sloughed senescent gastrointestinal cells, intestinal secretions, swallowed amniotic fluid with vernix caseosa, mucus from the rectum, and pancreatic secretions.[65] Passage of meconium *in utero* has traditionally been considered an indicator of acute intrauterine foetal distress, especially in relation to an asphyxial event.[66] However, in the late third trimester, some meconium staining is common and identified in up to 19% of placentas.[67] In addition, many instances of foetal hypoxia and distress are unaccompanied by meconium discharge.[68] With post-term pregnancies, the incidence of meconium staining increases, and there is a positive correlation with compromised pregnancy outcome. But even in this population, half of the post-term babies show no residual evidence of significant distress. Meconium discharge by a foetus less than 30 weeks of gestational age is extremely rare, even when prolonged intrauterine hypoxia has been documented.

The clinical significance of meconium relates to the duration of meconium discharge to delivery of the infant and placenta. The mere presence of meconium at the time of birth in a term pregnancy which is unaccompanied by staining of the placenta, correlates with acute meconium staining, and may not have clinical relevance. On the other hand, the prolonged presence of meconium *in utero*, characterised by progressively extensive staining of the placenta, correlates with subacute or chronic meconium staining and indicates a high risk of the foetus for meconium aspiration syndrome,[69] perinatal asphyxia, cerebral palsy or other central nervous system deficits.[30] In the Collaborative Perinatal Study of the 1960s, hypoxic/ischaemic disorders accounted for 18% of severe perinatal cerebral palsy. In this group, only 30% had a recognisable antecedent condition as described above. In the remainder, the injury was related to meconium, either from meconium aspiration syndrome or from direct toxic effects on the placenta. Prophylactic amnioinfusion with saline has been attempted in cases of thick meconium discharge, but the overall benefit of this procedure remains controversial.[70,71]

Meconium is toxic to the placenta, in particular to the membranes and umbilical cord. The amniotic epithelium, subjected to meconium exposure for several hours, undergoes degenerative changes characterised by columnarisation, formation of pseudopapillae, cytoplasmic vacuolation, and eventual necrosis and sloughing. The membranes become oedematous with easy slippage of amnion from chorion. The umbilical vein and chorionic surface vessels undergo contraction[72] and segmental mural necrosis with degeneration of the medial myocytes.[73] Meconium pigment may be identified in amniotic macrophages as soon as one hour after discharge,[74] and after four to six hours, may also be identified in chorionic macrophages.[75]

In summary, the consensus appears to be that meconium discharge may occur in the setting of foetal distress, or may simply be a reflection of foetal maturity. In the mid-trimester and postmature infant, *in utero* meconium discharge has a positive association with foetal compromise, but not all foetuses of these gestational age groups that have passed meconium will demonstrate significant sequelae. The distinction between acute,

subacute and chronic meconium exposure can, and should be made morphologically, since subacute and chronic meconium exposure have stronger association with poor pregnancy outcome than acute meconium discharge.

Abnormalities of the umbilical cord

The umbilical cord is the lifeline of the foetus, and consists of two umbilical arteries and the umbilical vein suspended within Wharton's jelly. The typical umbilical cord measures 50–60 cm at term. A spiralled appearance is normal, usually in a left helical direction, with a mean and standard deviation coiling index of 0.21 ± 0.07.[76] Umbilical cords with a left twist outnumber those with a right twist by 7 to 1.[77] There is no correlation with maternal or foetal handedness, and the reason for this may be that the right umbilical artery is usually larger than the left umbilical artery.[77]

Abnormalities of cord length are best determined through measurement at the time of delivery, since portions of the cord may be left attached to the infant, used for blood gas determinations or other measurements, or discarded. A length of at least 30 cm is usually necessary to prevent traction on the cord during vaginal delivery. Excessively short cords (those less than 30–40 cm in length) are seen in infants with syndromes associated with decreased foetal movement (e.g. trisomy 21, skeletal dysplasias)[78] and long-term neurological abnormalities.[79] There is also an association with developmental anomalies such as abdominal wall defects. Excessively long cords (those greater than 70–80 cm in length) are associated with foetal distress, cord entanglement, cord prolapse, true knots, hypercoiling, constriction and thrombosis. Infants with excessively long cords are at significantly-increased risk of abnormal neurological follow-up, and mothers with a history of an excessively-long umbilical cord are at increased risk of a second excessively-long cord.[35]

Abnormalities of the coiling index often reflect abnormalities in foetal activity, and are associated with adverse perinatal outcome, including increased perinatal mortality, intrauterine growth restriction and foetal distress. Hypercoiled cords may show stricture formation in cases of intrauterine foetal demise, and in the presence of signs of vascular obstruction, such as thrombosis, may be considered the cause of intrauterine death.[80,81]

Single umbilical artery (SUA) has an incidence of 1% in singletons and 9% in twins, and should always be looked for at birth. Foetal malformations are more common.[82] There is an association with growth restriction, maternal diabetes mellitus, antepartum haemorrhage, polyhydramnios and oligohydramnios. SUA may also be an isolated anomaly seen in otherwise perfectly healthy infants.

The insertion of the umbilical cord is normally central, paracentral or eccentric. Cords inserting at the edge of the placental disc (marginal insertion) and into the membranes (velamentous insertion) are more common in multiple pregnancies and in association with SUA. They are also found relatively frequently in early abortions and are highly correlated with congenital anomalies. Velamentous cord insertions result in the presence of membranous blood vessels which run along the free placental membranes unprotected by Wharton's jelly. Such vessels are vulnerable to injury, and are at risk of thrombosis or haemorrhage. Velamentous vessels located over the cervical os constitute the serious condition of vasa praevia, and pose the risk of rupture, haemorrhage and exsanguination during vaginal delivery.

Thrombosis of umbilical vessels occurs most frequently near term. They may develop due to velamentous cord insertion, acute funisitis, umbilical cord knotting, hypercoiling or torsion, amniotic bands, or maternal or foetal coagulopathies. Thromboses severely compromise the foetal-placental circulation, and lead to foetal injury or death.

THE PLACENTA AND OBSTETRIC LITIGATION

Obstetrics is a very high-risk medical specialty with medical liability insurance premiums for its practitioners reflecting this fact.[83] The developed world has seen a significant increase in the frequency of lawsuits directed against obstetricians when infants they deliver are found to have neurological disabilities, most commonly cerebral palsy. Commonly, the basis of litigation is the notion that such neurological disabilities are the result of failure or delay in intervention or inappropriate management of injuries believed to have occurred during the process of delivery. A massive increase in the intensity of foetal monitoring and changes in methods of delivery, including increased use of caesarean section,[84] have not substantially decreased the incidence of cerebral palsy.[85,86] One reason for this is that the vast majority of injuries occur before labour and hospital admission, and many are the result of intrauterine infection and inflammation, or reduced or interrupted placental vascular perfusion.[87] The majority of cases of cerebral palsy, particularly in term infants, are now known to be due to antepartum events.[88]

The issues of causation in relation to placental pathology are complex and often multifactorial. The pathological conditions of the placenta, including the umbilical cord, are increasingly recognised as playing important roles in the causation of such neurological impairment. Many of such conditions develop during the

Table V. Placental findings indicating acute and chronic *in utero* compromise.

Placental findings indicating acute *in utero* compromise
Normal placental weight or weight appropriate for foetal weight
Acute villous oedema
Intravillous haemorrhage
Acute retroplacental haemorrhage
Acute meconium staining
Placental findings indicating chronic *in utero* compromise
Abnormal placental weight in relation to foetal weight
Chorangiosis
Foetal normoblastaemia
Chronic meconium staining
Meconium-associated myonecrosis of cord vessel(s)
Acute or necrotising funisitis
Significant chronic villitis
Amnion nodosum
Significant placental ischaemia or infarction
Decidual vasculopathy
Maternal floor infarction/massive perivillous fibrinoid deposition
Chronic foetal vascular obstruction/foetal thrombotic vasculopathy

prenatal period, long before labour and delivery. Although they cannot be prevented by the best of obstetrical care, they can be identified and documented by formal pathological examination of the placenta.[89]

Pathological findings in the placenta may be helpful in understanding adverse outcome in one of two ways. Firstly, the placenta itself may be abnormal and thus contribute directly to the adverse outcome. Primary lesions of the placenta, such as massive perivillous fibrinoid deposition, decidual vasculopathy leading to placental ischaemia and/or infarction and large chorangiomas, fall into this category. Secondly, the placenta may harbour abnormalities that indicate the presence of an adverse intrauterine environment. An example is the presence of a sizeable intervillous haemorrhage within a placenta that is markedly pale and hydropic, and in which villous capillaries show the presence of nucleated red blood cells, indicating the presence of significant foetomaternal haemorrhage.

During legal proceedings, the pathologist functioning as an expert witness may be asked to specify a time frame for a placental lesion. It is often impossible to provide answers accurate to days or hours. Instead, it is often helpful to broadly distinguish between placental pathologies resulting in acute or chronic *in utero* compromise (Table V) as a framework for determining the timing of the foetal insult.

CONCLUSION

Clinically-relevant information is obtained in a large proportion of placentas when specimens are submitted for formal pathological examination following established guidelines. The placental pathologist is in a unique position of being able to diagnose diseases of the mother, foetus or newborn. These include conditions such as chorioamnionitis, subclinical gestational diabetes mellitus, impaired placental perfusion due to reduced uterine blood flow, and potential recurrent reproductive failure. Information obtained through pathological examination of the placenta may be useful in the clinical care of the mother and child, and in explaining past obstetrical history. When the outcome of a pregnancy is adverse, placental pathology may also be of utility in adjudicating the outcome of litigation.

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