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ABSTRACT

Rates of preterm birth range from 5% to 13% of deliveries in developed countries. About two-thirds of preterm deliveries are due to spontaneous onset of preterm labour or preterm premature rupture of membranes. Approximately one-third follow induction of labour or caesarean section performed for maternal or fetal indications such as preeclampsia, haemorrhage, non-reassuring fetal heart rate or intrauterine growth restriction. Thus, pathologists are frequently called on to evaluate preterm placentas, to determine the cause of the spontaneous preterm birth and/or correlate placental findings with the clinical history. This review provides pathologists with an overview of the recent clinical research in the pathogenesis of preterm birth and relates these to the correlative placental pathologies of the major causes of spontaneous preterm birth. A brief summary of the placental gross and histopathological findings in indicated preterm birth is also included.

Preterm births are those occurring at less than 37 weeks of gestation. They account for 12–13% of deliveries in the USA and 5–9% in other developed countries. Complications of preterm birth are significant; prematurity accounts for 75% of perinatal mortalities and more than 50% of long-term infant morbidities including neurological deficits, blindness, deafness and chronic lung disease. Moreover, rates of preterm birth in the USA have increased by 31% since 1981, with later preterm births (at 34–36 weeks of gestational age) comprising about two-thirds of this increase in recent years. Survival and adverse cognitive, organ functional, and motor outcomes are inversely related to gestational age; the highest rates of adverse outcomes are seen in the extremely preterm (<28 weeks of gestational age) and severely preterm (28–31 weeks of gestational age) infant. However, even late preterm infants born between weeks 32 and 36 of gestation have increased rates of infantile thermolability, respiratory insufficiency and chronic lung disease, feeding difficulties and necrotising enterocolitis, and neurological sequelae including periventricular leukomalacia. Later in childhood, the prematurely born infants have reduced motor, speaking, writing, mathematical and behavioural skills, compared to children born at term. The costs of prematurity have been calculated to be over $10 billion in the USA.

The causes of singleton preterm birth are incompletely understood, and a full discussion of the current clinical literature on this subject is beyond the scope of this review. However, an overview is presented. Clinically, the single greatest risk factor for spontaneous preterm birth is a maternal history of prior preterm birth, especially multiple and/or early preterm birth(s). When a woman has had a prior preterm delivery, her risk for repeat preterm delivery is some two- to five-fold higher, depending on the presence of other potential risk factors. Detectable maternal cervicovaginal fetal fibronectin levels (a marker of choriodecidual disruption after 24 weeks) of gestation and short cervical length (less than 25 mm in an asymptomatic woman at 24 weeks) are other highly predictive risk factors. Additional significant risk factors include a history of prior uterine instrumentation(s) and raised serological phosphorylated insulin-like growth factor binding protein-1 levels. Recent studies have indicated that there are also important, independent socioeconomic, racial, and familial genetic risk factors for the occurrence of preterm birth; for example, African American women have about a two- to four-fold greater rate of preterm deliveries than do whites, and economically disadvantaged women have twice the rate of preterm births over women who are not poor. Hispanics and East Asian women have low rates of preterm birth. Preterm birth, in whites, is more often preceded by preterm labour; in blacks, by preterm premature rupture of membranes. Other clinically identified or suspected risk factors, singly or in combination, are: extremes of (low or advanced) maternal age; maternal stress, depression, anaemia or substance and/or tobacco abuse; absence of prenatal care; and periodontal disease. Maternal smoking throughout pregnancy is associated with a two-fold risk for preterm birth, and the increased risks associated with periodontal disease appear to most closely correlate with its severity.

Preterm birth has been clinically categorised as: (1) spontaneous preterm birth (SPTB), which, in turn, follows (a) onset of preterm labour (PTL) (regular contractions with accompanying cervical change and intact membranes, and accounting for 40–45% of cases of preterm births) or (b) preterm premature rupture of membranes (PPROM) (spontaneous rupture of membranes at less than 37 weeks of gestation at least one hour before the onset of contractions, and seen in 25–30% of preterm births); and (2) indicated preterm birth (IPTB), wherein labour is induced or caesarean section performed for maternal or fetal reasons that include maternal preeclampsia and haemorrhage, and fetal non-reassuring heart rate or intrauterine growth restriction (IUGR). Of note is that there is a large body of evidence that the normal, term process of parturition involves a cascade of activations of cellular components and mediators of an inflammatory pathway(s) that results in onset of labour and membrane rupture.
that, while PTL and PPROM are separate clinical scenarios, they are likely the pathological outcomes of abnormal microbial and non-microbial activation of and/or induction of imbalances among these normally well-timed and orchestrated components and mediators. In the discussions that follow, non-microbial aetiologies appear more prevalent in PTL. Clinical interventions to reduce the incidence of preterm birth have largely been directed at targeting treatment for individual risk factors and at answering clinical questions rather than pathogenic mechanistic ones, and have not been very successful.

The above facts reveal that the pathologist is and will be increasingly asked to examine placentas from preterm births in order to help explain the occurrence of PTL or PPROM in given instances. Also, since low birth weight (for gestational age (IUGR) or due to preterm birth) is a recently recognised risk factor for the development of chronic adult disorders such as hypertension, diabetes mellitus, and atherosclerotic cardiovascular disease, placental examinations from cases of preterm birth may well provide valuable clues for predicting which infants and why some infants may be at relatively greater risk for developing these long term complications. The aim of this review is to present sufficient pathogenic background concerning what is currently appreciated about the microbial and non-microbial causes of SPTB, together with an update in the placental pathological features of SPTB, in order that the practising pathologist will be able to make diagnoses that will contribute to care of and knowledge about the risks facing the newborn. The review may also contribute to understanding the complex and multifactorial pathogenesis of non-microbial causes of SPTB and IPTB.

THE ROLE OF INTRAUTERINE INFECTION IN SPTB

Intrauterine infection is clinically a frequent aetiology of preterm birth following PTL and PPROM, and it is most prevalent and severe in cases of earlier preterm birth. Clinically, the most common pathogens are the genital mycoplasmas (especially Ureaplasma urealyticum) and Streptococcus agalactiae, Escherichia coli, Fusobacterium sp., and Gardnerella vaginalis. Group B streptococcus, Staphylococcus, Propionibacterium, Pseudononas, Proteus and Klebsiella species have also been commonly associated with acute clinical or pathological chorioamnionitis. Candida albicans, while an uncommon pathogen, has been associated with high rates of morbidity and mortality in early preterm infants. Many of these have been associated with bacterial vaginosis, a condition in which the normal vaginal flora of lactobacilli are replaced by other low and high grade pathogens. However, the exact rates of infection and factors that determine a given maternal–fetal dyad’s susceptibility to infection and SPTB are unclear. Microbiological studies of amniotic fluid have shown that overall rates of infection in preterm birth are 25–40%; some 32.5% of women with PTL and delivery and over 75% who deliver following PPROM have positive amniotic fluid cultures. Molecular microbiological techniques have indicated, however, that even the high observed rates of positive cultures substantially underestimate the true rates of microbial invasion of the amniotic cavity, since women with negative amniotic fluid cultures have amniotic fluids that are positive for microbial footprints (ie, bacterial 16S rRNA by PCR methodology). Also, women with negative amniotic fluid cultures for U urealyticum, but positive U urealyticum PCR, have comparable rates of preterm deliveries to women with positive amniotic fluid cultures for this organism. Studies have additionally shown that infection can be confined to the decidua and that the rate of chorioamnion colonization is twice even that of the amniotic fluid.

Although the above indicates that bacterial infection is very common and predisposes to preterm delivery, not all women with positive evidence of bacteria in the chorioamnion have PTL or PPROM; up to 70% of women undergoing elective caesarean section at term have evidence of bacterial invasion and even inflammation. As noted above, there is mounting evidence indicating that the process of normal term parturition involves activation of complex inflammatory components and mechanisms that lead to labour and membrane rupture. Evidence also indicates that preterm birth results from pathological activation of these inflammatory factors. The relative numbers and pathogenicity of the organisms gaining access to the uterine or amniotic fluid cavities, together with the degree of underlying maternal inflammatory response and predisposing genetic, cervical/structural risk factors and/or fetal factors may “tip the balance” of these inflammatory mechanisms, involved in normal parturition, towards PTL or PPROM and preterm delivery. There are, however, investigators who submit that chorioamnionitis may develop as a consequence of PTL rather than representing a cause of preterm birth, based on the observation that 10–15% of placentas at term have histological acute chorioamnionitis (HCA).

Figure 1  Histological chorioamnionitis maternal inflammatory response. (A) Stage 1 maternal inflammatory response of the chorionic plate is shown. Neutrophils are linearly aligned in the subchorionic space and present in the trophoblastic epithelium underlying the chorion. (B) Stage 2 chorioamnionitis. (C) Stage 3 with severe inflammation and amniotic necrosis; residual necrotic amniotic epithelial cells are seen.
PLACENTAL PATHOLOGY IN SPTB
Not surprisingly, given the above, studies to date⁴⁷ have shown that there is poor correlation between clinically diagnosed chorioamnionitis and the pathological diagnosis of HCA. This may be partly due to the fact that the clinical definition of chorioamnionitis is non-uniform, and that most cases of histopathological chorioamnionitis represent subclinical infection.⁶⁹⁸⁹ Research into the pathogenetic mechanisms involved in infection in extreme–severe preterm birth 31 do more closely correlate with the high prevalence of HCA in this population.⁶⁹⁷⁵ Research into the pathogenetic mechanisms involved in infection in extreme–severe preterm birth may provide future clinicopathological explanations and improved correlations. For example, a recent murine model study of intrauterine infection has provided evidence that activation of toll-like receptor-4 (toll-like receptors recognise microbial ligands and host products that are released during tissue damage) by Fusobacterium nucleatum, and not the bacterium itself, is responsible for the organism’s ability to colonise and incite a necroinflammatory response in the placenta and result in fetal loss.⁹⁹

Acute chorioamnionitis
Gross examination of the placenta is addressed by Kaplan in this issue,⁶⁶ but briefly, evidence of chorioamnionitis may be manifested as membranous oedema, clouding, or yellowish-green discolouration and congestive placentomegaly. The cord may show punctate yellowish lesions characteristic of candidiasis (discussed below), although minute whitish lesions may rarely be seen in severe bacterial infections.⁴⁷⁄⁷⁶

The staging (stages 1–3) and grading (grades 1–2) of HCA have been standardised by Redline et al.⁷² HCA is fundamentally a maternal inflammatory response that begins in the decidua of the external membranes as patchy deciduitis and progresses to margination of neutrophils along the deciduochorionic junction and, additionally, in the subchorionic maternal space as linear aggregates beneath and within the trophoblast (stage 1, early). Stage 1 is generally clinically silent. Stage 2 (intermediate) is characterised by subsequent inflammatory infiltration into the chorion of the placental membranes and chorionic plate, and stage 3 (advanced, late) by full thickness chorioamnionitis inflammation with amniotic necrosis and denudation, neutrophilic karyorhexis, and/or accumulation of fibrinopurulent debris (fig 1A–C). Stages 2 and 3 are associated with increased risk of neonatal morbidity and mortality; stage 2 is most common in all preterm births, but especially in the earliest periods of gestation.⁴⁶ Maternal grade (intensity and distribution of inflammation) 2 of subchorionic neutrophilic aggregation, characterised by microabscess formations of at least 10 linearly arranged subchorionic cells with a 20 cell “depth”, in three or more foci, or in a confluent pattern, is associated with increased risk of neonatal infection.⁴⁷⁄⁷⁶ Application of these criteria helps the pathologist to avoid overcalling “aggregates” that represent artefact resulting from tangential section of the chorionic plate (fig 2A,B).

The fetal inflammatory response to infection is manifested by migration of neutrophils from chorionic plate vessels (termed acute vasculitis, although the inflammatory cells are not primarily directed at the vessel walls themselves) and from the umbilical cord vessels (phlebitis and arteritis of one or both arteries.) Fetal stage 1 and grade 1 (early inflammatory response) are applied to intramural chorionic vasculitis and/or phlebitis (fig 3A); fetal stage 2 (intermediate inflammatory response) to funisitis with arteritis or trivasculitis (fig 3B); and stage 3 (advanced response) when neutrophils and/or karyorhectic debris are present in arcs in the subamniotic region of Wharton’s jelly. Stage 3 is referred to as necrotising funisitis (subacute) (fig 3C1–2). Fetal grade 2 (severe) inflammatory response is characterised by severe infiltration of the cord or chorionic plate vessels (fig 4A,B) and may be accompanied by acute mural non-occlusive thrombosis. Prolonged intrauterine infection and severe fetal response (stage 3, grade 2) may be evidenced by mineralisation of the inflammatory and debris laden arcs in necrotising funisitis (fig 4C1–5) Chorionic villous oedema may also be prominent, with fetal grade 2 histopathology.

There are numerous important pathological outcomes associated with fetal stages 2 and 3 and fetal grade 2, particularly for

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**Figure 2** (A) Maternal inflammatory response, grade 2, with subchorionic microabscess formation. (B) This same response may be seen in the placental membranes.
extremely–severely preterm infants. Fetal stages 2 and 3 generally indicate increasing duration and/or severity of the infection; fetal grade 2, in particular, is strongly correlated with the presence of high fetal levels of circulating proinflammatory cytokines and inflammatory mediators, such as interleukin (IL)-6. This condition is referred to as the fetal (systemic) inflammatory response syndrome (FIRS/SIRS). FIRS is associated with increased risk of pulmonary complications including bronchopulmonary dysplasia, necrotising enterocolitis, and neurological injury including cystic periventricular leukomalacia and cerebral palsy. Raised cytokines have been shown experimentally to affect the brain directly by a toxic effect on the oligodendroglia and indirectly by endothelial and macrophage activation, which leads to increased capillary permeability, microthrombosis, and elaboration of macrophage-derived cytotoxic factors.

The presence of non-occlusive mural thrombi in chorionic plate or cord vessels has been associated with increased risk of fetal thromboembolic phenomena in term infants. In addition, chorionic villous oedema, potentially even without intense chorionic vasculitis, has been linked to increased risk, in extremely low birth weight (ie, extremely preterm) infants, for cerebral palsy and impaired neurological function when these children reach school age. Thus, as was proposed by Naeye et al in 1983, chorionic villous oedema is potentially an independent histopathological feature associated with increased risk for morbidity and mortality in preterm infants. The chorionic villous oedema may reflect fetal cardiac dysfunction or local chorionic villous factors and increase villous hydrostatic pressure and impair fetal villous capillary perfusion. In a study by Redline et al, only histological acute chorioamnionitis with a severe fetal vascular response decreased the association of villous oedema with low cognitive test scores in childhood in one of two neurological assessment analyses.

Certain organisms have been more strongly associated with both intense chorionic plate inflammation and fetal vasculitis, including the following: Actinomyces species; Prevotella bivia; Corynebacterium species; Escherichia coli; Peptostreptococcus magnus; group B, group D, alpha-haemolytic, and anaerobic streptococci; Mycoplasma species; and Ureaplasma urealyticum. However, it should be remembered that group B streptococcal infection is not consistently accompanied by significant inflammation.

Subset of acute chorioamnionitis with peripheral microabscesses of the umbilical cord
As shown by Kaplan (this issue), the classic gross finding is the presence of pinpoint yellow-white nodules on the umbilical cord that track the coils of the underlying vessels. They are best viewed with tangential light and/or use of a hand-held magnifying lens. These foci correspond to histological sub-amniotic microabscesses (fig 5A,B); subacute necrotising funisitis may also be seen in infections of longer duration, and...
include mineralisation of the arcs of inflammatory detritus, and cord vessel thrombosis in more chronic cases. The vast majority of these cases are due to *Candida albicans* but *C parasilopsis* and other species have been identified. (Co-infection with bacteria and genital mycoplasmas may also occur.) Intrauterine infection by *Candida*, although a less common cause of HCA, is more prevalent in preterm deliveries and is associated with significant mortality rates in the extreme and severely preterm infant. Gross detection of these lesions at the pathology bench should prompt rapid notification of the paediatrician/neonatologist caring for the newborn, with follow-up report of results of special fungal stains of the lesions, so that the timely administration of antifungal therapy can be instituted, if necessary. Rarely, the cord lesions represent foci of reaction to *Corynebacterium, Haemophilus* or *Listeria monocytogenes*. but, since so few placenta are cultured at delivery or at the pathology bench, these cord lesions may be due to infections by additional types of bacteria.

**Additional Acute Inflammatory Placental Pathology of Infectious Aetiology in SPTB**

**Subacute Chorioamnionitis**

This is a histopathological diagnosis characterised by a chorionic mononuclear (histiocytic) infiltrate admixed with degenerating neutrophils and karyorrhectic debris that is most prominent in the upper zone of the chorionic plate and indicates a more prolonged duration of intrauterine infection. It may represent infection by organisms of low pathogenicity or recurrent mild infection; clinically it is seen in gestations complicated by repeated second and/or third trimester episodes of bleeding. It was first proposed as a diagnostic entity by Ohyama et al in their report of 90 preterm placenta from deliveries at 23–32 weeks of gestation that had maternal stage 3 HCA. They concluded that subacute chorioamnionitis was strongly associated with the development of chronic lung disease (of infancy) and that (very) low birth weight and amniotic necrosis were the strongest predictors of this pulmonary outcome. However, since amniotic necrosis is seen in maternal stage 3 HCA, the relative significance of this histopathology, as it relates to chronic lung disease and other adverse outcomes awaits further investigation.

**Acute Villitis**

This acute inflammatory response is characteristic of haematogenous (transplacental) spread of infection from the mother to the fetus, and is overwhelmingly due to *Listeria monocytogenes*. *L monocytogenes* is a ubiquitous, facultative anaerobe that can survive and replicate within a broad thermal range; maternal infection is generally acquired through ingestion of contaminated food products (ie, vegetables, packaged or refrigerated delicatessen meats, dairy products). The organisms possess a variety of properties and virulence factors that enable them to cross intestinal–mucosal and blood–brain barriers, and they are more infective in immunocompromised hosts (ie, pregnant women and fetuses). They gain access to the maternal bloodstream and, in early infection, the intervillous space contains aggregates of (maternal) neutrophils admixed with fibrin. Acute villitis with marked microabscess formation and necrosis follows [fig 6A–C], since the trophoblast has receptors for the bacterial surface antigen internalin A, and cell-to-cell translocation of the bacteria across the placental barrier into the villous endothelial cells and fetal circulation occurs. Foci of acute intervillositis/villitis may coalesce to form punctate or confluent regions of abscess and necrosis that are grossly discernable on placental transmural sections. Detection of such placental lesions should prompt immediate notification of the neonatologist, since *L monocytogenes* is associated with rapid and disseminated fetal infection and high perinatal mortality. In addition, the lesions should be cultured, since investigations of perinatal death and epidemics may require detailed documentation through specific typing of the organism. Tissue Gram stains will show numerous, short Gram positive rods. Fecal contamination may result in ascending infection, with chorioamnionitis, but HCA is generally seen accompanying striking placenta, and haematogenous spread of the organism predominates. Finally, although the source of the neutrophils has not been investigated, given the contiguous appearing and florid response characterising acute intervillositis/villitis, it is likely that they are largely of maternal origin.

Other rare causes of acute villitis/intervillositis reflect maternal exposure to the pathogens. Acute fibrinopurulent intervillositis/villitis due to *Chlamydia psittaci* will show organisms within syncytiotrophoblast and a maternal history of exposure during assisted delivery of infected livestock may be obtainable. Maternal tularemia following tick or deerfly bite, inhalation of airborne bacteria, or ingestion of or contact with infected rodents or rabbits can lead to a severe villitis and fetal necrosis.

**Figure 4** Fetal inflammatory response, grade 2. (A) Intense inflammation of an umbilical artery along with necrotising funisitis (fetal stage 3). (B) Grade 2 response in a chorionic plate vessel.
Coccioides immitis spherules produce an intense villitis/intervillositis but rarely transplacental infection of the fetus. Fetal sepsis due to Escherichia coli and group B and other streptococci can be evidenced by neutrophilia within the fetal chorionic villous capillaries that may “spill out” into the stroma forming aggregates in the subtrophoblastic space. In contrast to L monocytogenes, there is little intervillositis or necrosis (fig 7).

**CHRONIC INFLAMMATORY PLACENTAL PATHOLOGY OF INFECTIOUS AETIOLOGY IN SPTB**

Chronic infections that may result in SPTB are largely those represented by the TORCH mnemonic (Toxoplasmosis, Others, Rubella virus, Cytomegalovirus, and Herpes simplex virus); all of these result in fetal onset of growth restriction, hepatosplenomegaly, cytopenias, coagulopathies, and, often, fetal hydrops and high infant morbidity and mortality. The TORCH infections cause chronic villitis, but the overwhelming majority of infectious chronic villitis in the United States is due to cytomegalovirus (CMV) and Treponema pallidum in (approximately 90%). However, herpes simplex virus (HSV), occasionally varicella zoster virus and poxviruses, and rarely rubella virus in non-vaccinated populations may be responsible. Parasitic pathogens are uncommon but may complicate gestations of women who have infected cats, are immigrants, or have travelled abroad and were exposed early in their gestation to endemic pathogens such as Toxoplasma gondii and Trypanosoma cruzi. Toxoplasma gondii is the most important parasitic placental infection in Western countries, and T. cruzi infection (Chagas disease) is endemic in parts of South America.

**CMV placitis**

CMV infection usually results in a boggy, pale, hydropic-appearing placenta and preterm delivery frequently complicated by placental abruption. In these instances, bulky and dysmature villi are seen at low power on light microscopy. More chronic infection generally results in a normal weight to shrunken, firm, pale, fibrotic placenta and fetal intrauterine growth restriction. However, in each case, CMV infection is characterised by lymphohistiocytic and especially, lymphoplasmacytic villitis. Plasma cell infiltrate, while not specific for CMV, is highly suggestive of CMV, especially if plasma cells are seen in terminal villi that are not in contiguity with the basal plate (see Chronic villitis of unknown aetiology, below). Intranuclear or cytoplasmic trophoblastic epithelial, Hofbauer cellular, and endothelial inclusions are easily seen on H&E stains in instances of clinically apparent disease in the infant. Thus, presence of stromal haemosiderin deposition (due to capillary damage), dystrophic mineralisations (“tombstones” of infected cells and villous damage), and sclerosis are virtually pathognomonic of CMV, even if viral inclusions are unapparent. However, immunoperoxidase stains for CMV are particularly useful in cases of longstanding intrauterine infection where the inclusions are sparse (fig 8A–E). The author recommends immunostaining...
four transmural sections, particularly if sclerosis is prominent. Use of PCR for CMV early and late antigen gp 64 has also been reported.61 Lymphoplasmacytic deciduitis in the capsularis and basalis is generally present. Of special importance to pathologists are the facts that prior maternal infection with CMV does not confer absolute immunity and that, overall, most cases of congenital CMV are due to recurrent maternal infection that is asymptomatic in both the mother and the newborn. Maternal immunity is associated with a 0.15–1% risk of vertical transmission of CMV (versus 40% in primary CMV infection); infected infants, while asymptomatic, have a 1% risk for developing sensorineural hearing loss.26 Since recurrent CMV is more common than primary CMV infection during gestation, placental examination in SPTB emerges as a critical means of detection of congenital CMV infection.

**Syphilis placentitis**

The histopathology of *T pallidum* is nearly as protean as its clinical manifestations. Although it may be limited to bulky, villous oedema and hypercellularity, T-lymphocytic and sometimes lymphoplasmacytic chronic villitis are typically seen in conjunction with sclerosis and circumferential vascular thickening of stem villous vessels and thrombosis. Thrombi are also seen in umbilical cord and chorionic plate vessels, and confirmatory Warthin–Starry or Steiner silver stains are best performed on the umbilical cord because of its relative hypocellularity. Recently Kapur et al determined that the T-lymphocytic infiltrates were of maternal origin in syphilis.39 Of note, the T-lymphocytic infiltrates due to *T gondii* and *T cruzi* have also been determined to be of maternal origin.70

**HSV**

HSV infection is characterised by lymphohistiocytic inflammation but marked necrosis and intervillitis, with trophoblastic multinucleation and viral cytopathy. The villitis/intervillitis is similar to that seen in *L monocytogenes* except that the inflammation is overwhelmingly chronic and trophoblastic glassy inclusions are present. Intranuclear inclusions are confirmed as HSV by immunoperoxidase stains (fig 9A–C). About 95% of intrauterine HSV infections are due to acute ascending infections from the maternal genital tract, and most occur with intact membranes. Therefore, amniotic multinucleation and necrosis is present and, frequently, lymphoplasmacytic chorioamnionitis. In more chronic cases these multinucleated

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**Figure 7** Acute villitis with fetal sepsis. Sections from a case of preterm PROM and neonatal sepsis due to *Escherichia coli* show neutrophils in the chorionic villous capillaries and villous stroma. Vascular lumina on the left aspect of the image show aggregates of bacteria due to bacterial overgrowth. (Material generously provided by Dr D Heller, University of Medicine and Dentistry of New Jersey, Newark, New Jersey, USA)

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**Figure 8** Chronic villitis due to cytomegalovirus. (A) Low power image showing chorionic villous dysmaturity, patchy villous sclerosis, and chronic villitis. (B) Higher magnification confirms the presence of stromal lymphoplasmacytic infiltrate. (C) Chorionic villus shows lymphoplasmacytic villitis, iron deposition, and cytomegalovirus (CMV) inclusions, denoted by black arrow. (D) High power shows classic CMV inclusions in villus. (E) Several inclusions stain positively by immunoperoxidase stains for CMV.
residual cells may be incorporated into the superficial chorion. Chronic lymphoplasmacytic villitis is accompanied chronic deciduitis. Some 5% of intrauterine HSV infections represent primary haematogenous transmission.

**Chronic decidual inflammation of probable infectious aetiology**

Chronic deciditis, isolated to the decidua basalis, and defined as diffuse lymphocytic infiltrate of the basal plate or any infiltrate in the decidua basalis that includes plasma cells is abnormal (Fig 10). It is believed to represent maternal response to chronic intrauterine colonisation or infection by organisms of low pathogenicity and may predispose to preterm delivery. Potentially, infection may develop early in gestation, before membrane fusion of the chorioamnion of the gestational sac to the opposite uterine wall, at 19–20 weeks, and then later after fusion, transmitted to the conceptus. Alternatively, the inflammation may represent recurrent/persistent low-grade infection that exists between pregnancies as chronic endometritis. Redline has identified it as a risk factor for recurrent pregnancy loss. In a recent study of endometrial microbial colonisation and chronic endometritis in women who were 5 months post-partum, Andrews et al found similar rates of colonisation in women with history of SPTB at less than 34 weeks (85%), IPTB at less than 34 weeks (79%), and spontaneous term birth (81%). They concluded that the infection and inflammation did not confer greater risk for preterm birth in subsequent pregnancies. However, Edmondson et al found that 40% of preterm placentas from cases of idiopathic PTL and 15% of their control cases had chronic deciduitis; they determined that chronic deciduitis plays a role in some cases of PTL. Further clinicopathological studies may improve our understanding of the implications of this entity.

**PLACENTAL PATHOLOGY OF NON-MICROBIAL PROCESSES IN SPONTANEOUS PRETERM LABOUR**

The pathogenesis of spontaneous preterm labour in the absence of infection may also involve activation of pathways responsible for normal onset of labour via elements of the maternal and fetal hypothalamic–pituitary–adrenal axis. These include loss of the normally temporally coordinated interactions and changes in systemic and/or local uterine balances of oxytocin levels, fetal cortisol levels, and decreasing oestrogen to progesterone ratios. An important pathway also appears to involve non-infectious, pathological activation of decidual inflammation by decidual bleeding. Other “non-infectious triggers” of spontaneous PTL are uteroplacental ischaemia and/or oxidative stress, excessive uterine stretching, immunologically-mediated processes and uterine anomalies.

**Associated placental pathology**

Extravasated blood is a biochemical irritant. Clinical findings suggest that pathological findings of chronic, thin,
retromembranous haemorrhage and marginal haematoma may have causal implications, in settings of PTL.

**Chronic retromembranous haemorrhage (fig 11 A–C)**

While evidence of old decidual haemorrhage is not a specific finding for preterm labour per se, it was much more frequently identified in a large study of consecutively evaluated placentas from gestations of less than 32 weeks in duration; haemosiderin was seen in 43% of preterm placentas versus 0.8% from term gestations, and in 36% of the cases with preterm labour. The underlying cause of retromembranous haemorrhage may involve ischaemia and/or endothelial damage. Decidua capsularis ischaemia should be especially suspected if there is laminar necrosis or leukocytoclastic necrosis. Immunoperoxidase staining for complement component 9 and nitrotyrosine residues (markers of oxidative stress) were prominent in membrane rolls with laminar necrosis, in the study of uteroplacental hypoxia by Stanek et al. The presence of tumour necrosis factor α (TNFα) was not evaluated in their study, but TNFα production is a common outcome of activation of monocytes/histiocytes by a multitude of stimuli, including tissue damage from ischaemia and bacteria, immune complexes, toxins and other cytokines. TNFα causes release of proteolytic enzymes from mesenchymal cells, in addition to causing aggregation and activation neutrophils. TNFα has also recently been shown to raise apoptosis of cultured villous trophoblasts, and may have similar effects on extravillous trophoblasts. Alternatively, it may be that extravillous trophoblasts are signalled to again elaborate or increase TNFα production which acts to induce decidual vascular smooth muscle apoptosis and elastin degradation, in a manner noted for first trimester trophoblasts and in decidua vascular smooth muscle apoptosis and elastin degradation, in a manner noted for first trimester trophoblasts and in other inflammatory cytokines, matrix metalloproteinases involved in amnion degradation, and mediators of increased uterine toxicity (ie, prostaglandin production by amnion, decidua and myometrium), and may play a role in cervical ripening. In addition, TNFα administration can induce parturition in animals, and anti-TNFα administration to pregnant mice has been shown to significantly reduce rates of PTL and stillbirth. These observations support the hypothesis that preterm parturition is a pathological condition that is at least partly mediated by the deleterious effects of TNFα; blacks may have a predisposition for PTL due to differences in gene expressions for TNFα-receptor, which may affect its synthetic rates and/or half-life. Additional cytokines and chemokines such as IL-1β, IL-4, IL-6, IL-8 and factor Va are implicated in preterm birth and seem to also exhibit racial differences and polymorphisms, but their precise roles and points of entry in the cascade of preterm labour are unclear. Esplin et al. identified 56 different differentially expressed human myometrial transcriptomes associated with term labour and confirmed four as specifically up-regulated. They then evaluated levels of monocyte chemotactic protein-1 expression (MCP-1) in gestational myometrium in term and preterm labour, in the absence of clinical chorioamnionitis, placental abruption, and arrest and other abnormalities of labour. They proposed that MCP-1 is a common link in the chain of normal and preterm labour (both of which are accompanied by an influx of inflammatory cells into the cervix and myometrium). Placental membranous chronic haemorrhage was not included in their study employing cDNA microarray analyses for the pro-inflammatory cytokine, but they noted that elevation of human myometrial transcripts of MCP-1 followed treatment of their in vitro media with TNFα, IL-1β and interferon-γ; it was significantly elevated with IL-1β. However, maternal demographics were not specified in this study.

**Marginal haematoma**

Marginal haematomas (MHs) are reportedly seen in 0.74–1.9% of placentas, but in the author’s experience, acute marginal hematomas are encountered in about 15% of serially examined placentas (unpublished observations); this may reflect the relatively large numbers of patients admitted to an academic setting.
maternal–fetal medicine service for complicated gestations and PTL and delivery. In one series, 29% of placentas from deliveries from 20–25 weeks of gestation, 19% from 26–31 weeks, and 17% from 32–36 weeks had (acute) marginal abruption. Evidence of chronic abruption (apparent chronic peripheral/marginal hematoma) was found in 7–10% of placentas from these weeks of gestation.

Clinically, MH may be seen on prenatal ultrasonogram and is referred to as “subchorionic haemorrhage” or “periplacental haemorrhage”. They may, if rapidly enlarging or recurrent and of great enough volume, lead to bleeding with preterm birth or spontaneous abortion, or they may be detected early in gestation and “resolve” and lead to

Figure 12  Acute marginal hematoma (MH). (A) The lateral placental margin (delimitated by a layer of decidua at the placental margin) is disrupted by acute haemorrhage that dissects into the chorionic villous parenchyma. (B) Example of large maternal venous vessels normally present at the lateral placental margin. The occurrence of MH is attributed to bleeding from these veins. (This image also shows acute villous congestion and intravillus haemorrhage; the villous findings and the exaggerated venous dilatation in this case are related to clinically diagnosed placental abruption.) (C) There is acute blood clot at the margin of this placenta, but no fibrin lamination, neutrophilic infiltrate or other evidence of organisation, and no parenchymal dissection. The accumulation of blood is incidental to delivery.

Figure 13  Chronic villitis of unknown aetiology (VUA). (A) VUA is best identified at low power scan. It is chronic lymphohistiocytic villitis that affects only a few villi and less than 5% of the total villi examined. Several left-central terminal villi are affected in this microscopic field. (B) High power photomicrograph, showing lymphohistiocytic infiltrate and villous destruction. (C) VUA characteristically involves the basal villi; chronic deciduitis is often present, as seen in this microscopic image. (D) Chronic chorioamnionitis is patchy; lymphocytes without plasma cells are seen in the lower chorion.
decidual necrosis: these are gross and histological criteria of
and lamination, polymorphonuclear infiltration and marginal
delivered of women with idiopathic PTL without antepartum
maternal space
the placenta, from thrombohematoma formation in the
subchorionic
thrombohematoma
used term "subchorionic haemorrhage", is different from
authors suggested, and others have agreed, 47 that the separation
was due to disruption of ectatic marginal uterine venous vessels
(fig 12A–C), and that haemorrhage of lower pressure accumula-
tion (in contrast arterial disruption in retroplacental hematoma)
had a role in the process of preterm labour.

Grossly, MH is crescent-shaped, reflecting its relationship to
the placental margin, and may extend for some distance over
the maternal surface. On section, the MH has a triangular
configuration at the lateral angle of the placenta; its base lies on
plane with the maternal surface, and its sides are respectively
formed by the lateral edge of the placental parenchyma and the
reflection of the fetal membranes. There is associated dissection
into the lateral chorionic villous parenchyma. MHs are usually
acute and affect less than a quadrant of the placental perimeter.
Incidental “MH” or passive, intrapartum accumulation of blood
in this anatomic crevice, with no grossly detectable loss of the
distinct border between the lateral placental margin and the
limits of the haematoma, may accompany oxytocin induction,
such as seen in indicated preterm birth. A recent or chronic MH
may produce a depression in adjacent marginal chorionic villous
tissue. The cut surface of chronic MH reveals laminated, friable,
yellowish-brown and/or calcified thrombohaematoma with
dissection of the lateral placental border; a superimposed acute
component may be present. Examination of suspected MH
should include a record of its dimensions and percentage of
marginal involvement; type of adherence and appearance;
features of chronicity; extent of dissection of adjacent parench-
yma on section; and type of associated, overlying membranous
insertion, along with histological evaluation of the junctional
region and membranes.24

Microscopic chronic haemorrhage in decidua basalis
The finding of haemosiderosis in the decidua basalis should
always be documented, but when seen in cases of PTL in the
absence of a clinical history of maternal hypertension, it may
have different implications and reflect a genetic or ethnic risk
factor.

PLACENTAL PATHOLOGY IN INDICATED PRETERM BIRTH
Induction of labour, with or without artificial rupture of
membranes, and caesarean section delivery in cases of indicated
preterm birth is largely performed for maternal hypertensive
disorders of pregnancy, and non-reassuring fetal heart rate and
IUGR. The pathology of the spectrum of pregnancy induced
hypertensive conditions as they relate to IUGR and the
placental pathology associated with IUGR is addressed by
Roberts and Post in this issue.78 These placental pathological
findings may be seen in preterm and term placentas. The other
orders that predispose to maternal indications for IPTB are
also largely related to those that result in underperfusion of the
placental bed and risk of IUGR, such as vasculopathy and
thrombosis associated with maternal primary hypertension or
diabetes mellitus (maternal vascular obstructive lesions). Thus,
there is some overlap between maternal and fetal indications for
indicated preterm delivery. However, there are some placental
pathologies that may not be associated with IUGR but with
"fetal distress" in the preterm fetus, and some that have been
found to be causally linked to IUGR, non-reassuring fetal heart
rate, and/or absent umbilical arterial end diastolic blood flow.
Although the following entities have also been described by
Roberts and Post, this section will focus on the placental
pathology that would more likely be seen in placentas from
induced or caesarean section deliveries performed for fetal
indications, and that might be expected to be identified in
different frequencies in late versus early preterm placentas.

Chronic villitis of unknown aetiology (VUA)
This is a common lymphohistiocytic villitis (5–15% of third
trimester placentas) that represents a subcategory of chronic
villitis, which, after extensive investigation, has not been proven
clinically or identified histopathologically to be due to infection
in the placenta, mother or infant. VUA affects terminal villi, ie,
those with vasculosyncytial membrane formation (morpholo-
geal feature of syncytiotrophoblast–endothelial cell basement
membranous apposition) characteristic of 52 or more weeks of
gestational development. Therefore, it must be underscored that
the diagnosis should be made with caution in preterm
placentas,79 and “restricted” to cases of 52–56 weeks.
Although placentas with VUA are often of low weight for
correlative periods of gestation and may have pale parenchyma
or punctate, firm lesions detectable by an experienced prosector,
VUA does not have consistent gross pathological features. VUA
is best detected at low power (20×), where its typical pattern of
subchorionic and, especially, basal villous inflammation and
overall involvement of less than 5% of the chorionic villi
becomes apparent (fig 13A). Because of its irregular distribution,
the detection of VUA is sample-dependent. However, about
90% of cases can be identified in the two to three histological transmural sections that are routine in most pathology laboratories (four sections may be optimal). Higher power view generally reveals small clusters of villitis affecting less than five villi (fig 13B). Plasma cells are rarely if ever seen, but, depending on the stage, the villitis may be accompanied by villous destruction, sclerosis, and the very rare, giant cell reaction. Lymphoplasmacytic deciduitis of the basalis and chronic chorioamnionitis, characterised by foci of small lymphocytic infiltrates in the lower chorion, may be seen (fig 13C,D). If the villous inflammation is patchy and involves more than 5% of chorionic villi, it is termed “diffuse VUA”. In diffuse VUA the midzonal parenchyma is generally not “spared”, perivillous fibrin deposition is seen, and villous destruction is more prominent (fig 14A,B). Most cases of VUA do not result in perinatal morbidity and mortality. However, there is a long recognised strong risk correlation between VUA and idiopathic IUGR. However, there is a long recognised strong risk correlation between VUA and idiopathic IUGR. The frequency of IUGR directly correlates with the extent of villous involvement; higher-grade, diffuse VUA with perivillous fibrinoid deposition correlates with severe IUGR, perinatal morbidity, and recurrent pregnancy loss. VUA has also been linked to unexplained (non-infectious spontaneous) preterm birth and perinatal asphyxia. The presence of VUA may contribute to placental insufficiency and to the oligohydramnios in gestations without a maternal hypertensive disorder or other risk factor. VUA with a diffuse distribution and inflammatory involvement of larger stem villi and villous vessels, termed “chronic villitis with obliterative vasculopathy”, is also more strongly associated with severe IUGR and perinatal morbidity, including neurological sequelae (fig 15A,B). The most important characteristic of VUA is that it appears to represent a localised, alloimmune process of “host versus graft” response in the chorionic villous tree from a breakdown in maternal–fetal tolerance. The lymphohistiocytic villous infiltrates in VUA have been shown to be composed almost exclusively of maternal CD8-positive T cells with a CD4:CD8 ratio of 0.1–0.5% and Hofbauer cells of fetal origin. Fetal Hofbauer cells are activated with up-regulation of major histocompatibility antigens and have a high rate of proliferation. The observations of activation and hyperplasia of fetal Hofbauer cells and focal syncytiotrophoblast destruction at sites of villitis, together with the absence of eosinophils and, essentially, of giant cells, are compatible with a delayed hypersensitivity response or a T-helper 1 type of response. The hypothesis that VUA is an alloimmune-mediated process is supported by its high risk of recurrence (10–25%) and 60% rate of reproductive loss in instances of recurrence. Not coincidentally, VUA is also more frequent in patients of high gravidity and in pregnancies affected by maternal autoimmune or alloimmune diseases. Obesity and diabetes mellitus may contribute to placentomegaly and greater trophoblast availability to maternal exposure and sensitisation. Recent studies indicate that maternal lymphocytes gain access to the fetal circulation (microchimerism) and that these are responsible for some infantile and childhood inflammatory disorders not formerly appreciated to be maternal alloimmune-mediated; T cells in juvenile myositis are of maternal origin. Moreover, maternal cells may persist in the peripheral blood of children for up to three decades.

**Massive chronic intervillositis**

This is most frequently seen in first trimester abortion, and therefore might be expected to be more prevalent in placentas from extreme and severe preterm birth (fig 16). It is a potential cause of IUGR in the preterm infant in IPTB or non-infectious SPTB, but in the author’s experience, it is rarely identified, and was not specifically noted among pathologies of preterm placentas in a four-year review by Redline. It is likely an alloimmune phenomenon, and it is unclear if it is a variant of VUA.
Fetal thrombotic vasculopathy

It is worth emphasising that the fetal/neonatal sequelae of fetal thrombotic vasculopathy (FTV) are related to the fact that vessels of the chorionic villous tree are in a continuous circuit with those in the fetus. The presence of chorionic villous thrombi leads to fetal thromboembolic phenomena and increased placental vascular resistance, and may lead to loss of end-diastolic blood flow, which may exacerbate any underlying cord or fetal factor(s) that predispose to thrombosis. FTV is a significant risk factor for thromboembolic neurological sequelae (ie, stroke). Other thromboembolic sequelae include limb reduction anomalies; systemic visceral thromboemboli in the gastrointestinal tract, kidneys, and liver wherein damage and hepatic thrombosis may lead to Budd–Chiari syndrome and perinatal liver disease; and renal vein thrombosis. IUGR with FTV is likely related to loss of functional placental parenchyma. In cases in which FTV is identified in several sections and/or chorionic plate and major stem villi, the placenta should be grossly re-examined to determine if venous and/or arterial vessels are affected and to ascertain what percentage of the chorionic villous parenchyma is affected (pale, firm, shrunken appearance with deep vessel thrombi or dilatation). The umbilical cord should also be re-examined for thrombosis. In addition, findings should be shared with the neonatologist/paediatrician, because a head ultrasonogram in the neonatal period may reveal pathology compatible with intrauterine stroke and can provide critical baseline information for subsequent comparisons.

Maternal floor infarction

Maternal floor infarction (MFI) (fig 17A,B) is associated with high rates of preterm birth (26–60%) and unexplained IUGR (24–100%); when of early onset, there is an associated increased risk of recurrence and severity in subsequent pregnancies. The dense cloaks of perivillous fibrinoid deposition impair villous exchange, resulting in villous atrophy; the aggregates alter blood flow patterns within the maternal space that may compromise function of “spared” villi. The aetiopathogenesis of the perivillous accumulation of fibrinoid in MFI is likely complex, but there is good evidence that it may be immune mediated.

CONCLUSION

The gross and microscopic examination of the placenta from preterm birth, whenever possible, should be approached with the clinical perspective of whether the specimen is from an SPTB or IPTB. Placentas from SPTB more commonly show acute chorioamnionitis with funisitis and intense vasculitis, marginal haematoma, chronic decidual haemorrhage, and acute and chronic infectious villitis. Placentas from IPTB more commonly show fetal thrombotic vasculopathy, those from late IPTB diffuse VUA and chronic villitis with obliterative vasculopathy, and those from early IPTB may show chronic intervillitis more frequently. All of these diagnoses have implications for the neonate and/or the mother. Further studies may reveal that maternal chorionic villous inflammatory cells, as seen in syphilis and toxoplasmosis, play a role in many other infectious villitides and that the effects of these cells contribute to the severity of the morbidity or mortality that has been largely attributed to the infectious organisms. Research may also reveal that the maternal lymphocytes in VUA and even infections may gain access to fetal circulation. The prolonged period that a woman’s lymphocytes may be in her child’s circulation may have implications for the aetiologies of other paediatric immune-mediated disorders. FTV may also predispose the infant to short or long term persistence of increased vascular tone or vascular disease, in addition to functional deficiencies of major organs such as the liver or kidneys. Thus, the placenta in preterm birth is not only a record of adverse conditions during intrauterine life that led to SPTB or necessitated an IPTB, it also likely holds clues to predicting which individuals will be at heightened risks for developing chronic diseases in childhood, or as adults. Therefore, pathologists are in a unique position to provide valuable observations that (1) may have immediate impact on the care of the premature newborn, (2) that, over time, may help explain the poorly understood pathogenetic mechanisms responsible for preterm birth, and (3) may potentially aid in the process of linking currently underappreciated roles of alloimmune-mediated processes and intrauterine stress to the development of chronic human diseases.

Figure 17 Maternal floor infarction. (A) Maternal floor infarction is characterised by dense perivillous fibrinoid deposition in the basal maternal space with associated involution and atrophy of the chorionic villi. This placental image is from a 26 week delivery of a growth restricted infant with non-reassuring heart rate and indicated preterm birth. There is a gradation of perivillous fibrinoid deposition that is most prominent in the basal region with diminishing “propagation” in its extension into the mid parenchymal zone. Chorionic villi in the basal region are ghost-like remnants; those in the upper regions are in varying stages of atrophy. (B) Higher power view shows chorionic villi in various stages of involution in almost direct proportion to the degree of perivillous fibrinoid deposition.
Take-home messages

- Preterm birth is common and is associated with high rates of perinatal morbidity and mortality; pathological examination of the preterm placenta can provide valuable information concerning the immediate and chronic risks for the infant and risks of chronic diseases in childhood.
- Risks of neurological sequelae in the infant have been linked to specific histopathological features in the placenta; the placental pathology report should include notation of these features.
- Spontaneous preterm birth due to preterm onset of labour and/or rupture of membranes likely results from abnormal activation a cascade of cellular components and mediators of an inflammatory pathway(s) that appear to be responsible for the process of normal, term parturition.
- Low birth weight infants are at risk for developing chronic diseases, in adulthood; pathological examination of the preterm placenta may provide important insights into future investigations to determine which infants will be at risk for development of cardiovascular disease, hypertension and diabetes mellitus, later in life.

Competing interests: None.

REFERENCES


