The placenta in preterm birth

O M Faye-Petersen

J. Clin. Pathol. 2008;61;1261-1275
doi:10.1136/jcp.2008.055244

The placenta in preterm birth

O M Faye-Petersen

Correspondence to:
Dr O M Faye-Petersen, The University of Alabama at Birmingham, North Pavilion 3547, 619 19th Street South, Birmingham, AL 35249-7331, USA; onafp@uab.edu

Accepted 13 August 2008

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[31] including neurological deficits, blindness, deafness and chronic lung disease.[12] 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.[17 83] The costs of prematurity have been calculated to be over $10 billion in the USA.[12]

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.[31] Detectable maternal cervicovaginal fetal fibronectin levels (a marker of choriodecidual disruption after 24 weeks) of gestation[17 31 37] 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.[17] 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.[17 21 30 31 65] 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[17 31 37]; and periodontal disease.[17 37] Maternal smoking throughout pregnancy is associated with about a two-fold risk for preterm birth,[32] and the increased risks associated with periodontal disease appear to most closely correlate with its severity.[37 50]

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 with 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).[31] 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.[14 62 79] Studies of the aetiology of SPTB indicate

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.[14 79] 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.[37]

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,[17 30 83] 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 pathogeneses 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*.[79] Group B streptococcus, *Staphylococcus*, *Propionibacterium*, *Peptostreptococcus*, *Pseudomonas*, *Proteus* and *Klebsiella* species have also been commonly associated with acute clinical or pathological chorioamnionitis.[29 35 52] *Candida albicans*, while an uncommon pathogen, has been associated with high rates of morbidity and mortality in early preterm infants.[66] 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.[31 35 79] 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.[31] 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).[79] 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 colonisation is twice even that of the amniotic fluid.[31]

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.[87] 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.[14 62 79] Evidence also indicates that preterm birth results from pathological activation of these inflammatory factors.[12–14 21 62 79] 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,[69] based on the observation that 10–15% of placentas at term have histological acute chorioamnionitis (HCA).

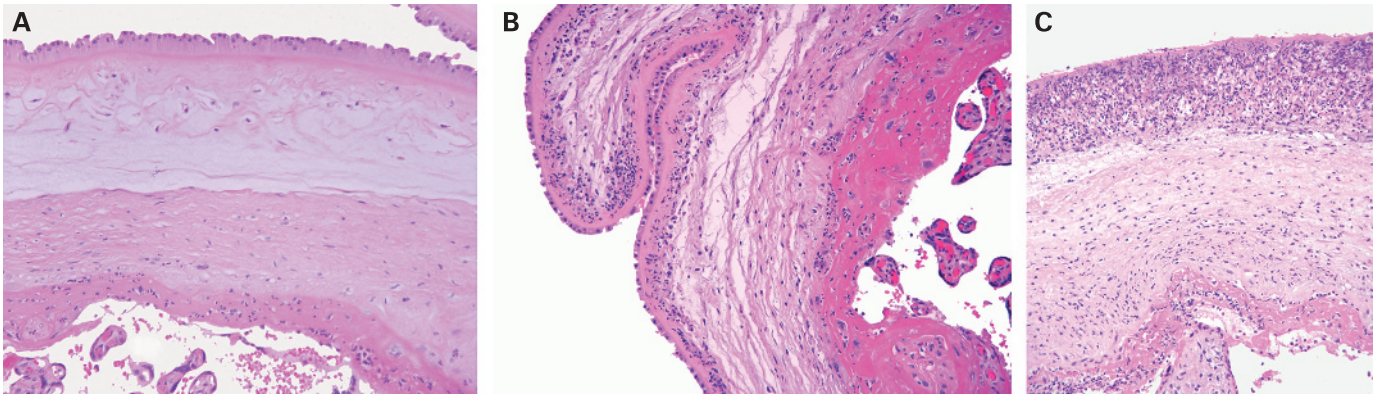

Figure 1 Histological chorioamnionitis maternal inflammatory response. (A) Stage 1 maternal inflammatory response of the chorionic plate is shown. Neutrophils are linearly aligned in the subchorionic space and present in the trophoblastic epithelium underlying the chorion. (B) Stage 2 chorioamnionitis. (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 date[47] 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.[94 95] In the study of very low birth weight infants by Redline *et al*, in 2000, only 9% of placentas with HCA had clinically diagnosed chorioamnionitis.[76] In the Alabama preterm birth study of gestations from 23 to 32 weeks, 12.8% of cases had clinical chorioamnionitis, 56.7% had positive placental cultures and 49.8% had histological chorioamnionitis/funisitis.[28] However, the clinically *estimated* prevalence rates of intrauterine infection in extreme–severe preterm birth[31] do more closely correlate with the high prevalence of HCA in this population.[69 89] Research into the pathogenetic mechanisms involved in SPTB 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.[49]

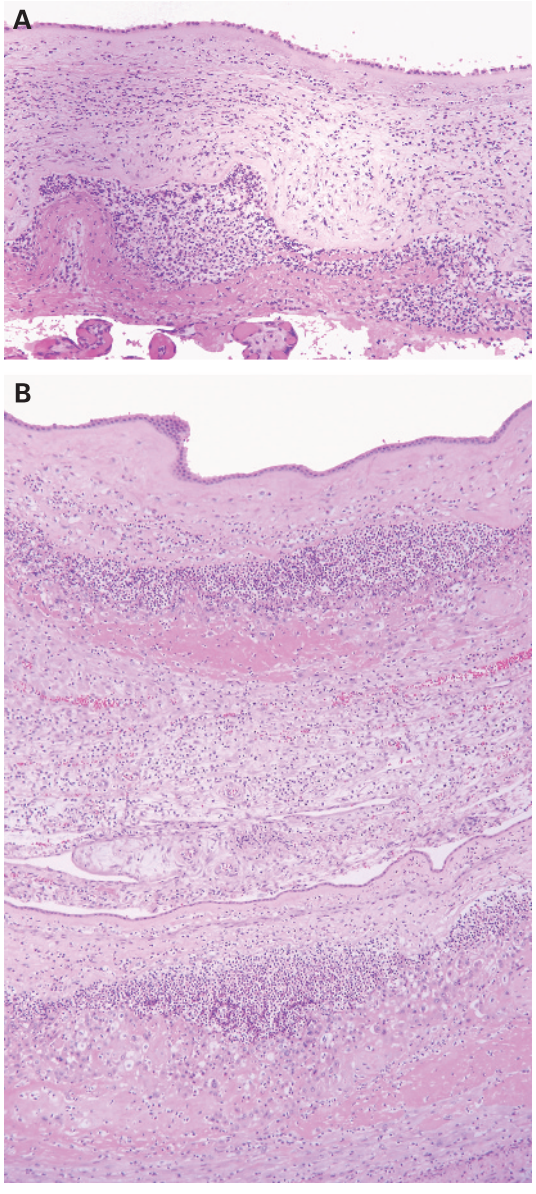

Figure 2 (A) Maternal inflammatory response, grade 2, with subchorionic microabscess formation. (B) This same response may be seen in the placental membranes.

Acute chorioamnionitis

Gross examination of the placenta is addressed by Kaplan in this issue,[96] 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 chorioamnionic inflammation with amniotic necrosis and denudation, neutrophilic karyorrhexis, 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 67] 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 karyorrhectic 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 inflammation 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 4C1–3) 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

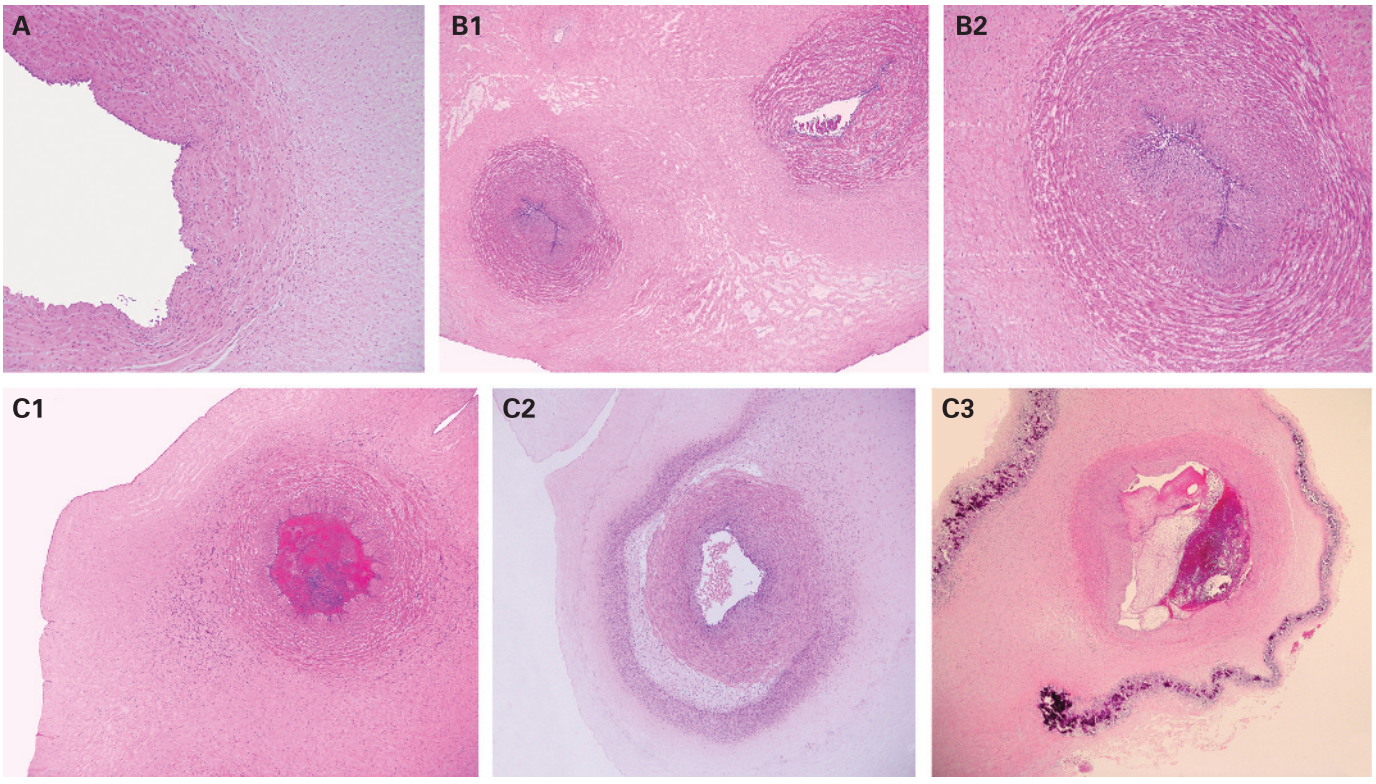

Figure 3 Fetal inflammatory response. (A) Stage 1 and grade 1 fetal inflammatory response with neutrophilic migration essentially confined to the wall of the umbilical vein. The vein is almost always the first cord vessel to show mural inflammation, but rarely, one of the umbilical arteries may first show a mural infiltrate. (B) B1: A low power section of cord with stage 2 and two vessels showing vasculitis. B2: A higher magnification of the artery showing early arteritis. (C) Stage 3 (subacute necrotising funisitis) is characterised by arcs of inflammatory cells in Wharton's jelly that exhibit a polarity towards the amniotic surface as a response to organisms and/or chemotactants in the amniotic fluid. C1: Early formation of inflammatory arcs around an artery; the vein shows prominent perivascular inflammation. C2: Necrotising funisitis of longer duration results in prominent inflammatory and karyrrhectic debris arc-like formations; necrotising funisitis around an artery is shown. Intense vasculitis (fetal grade 2) may be present. C3: In prolonged and severe intrauterine infections, typically with *Candida* or *T pallidum*, these arcs may mineralise and cord vessels may show mural thrombosis (fetal grade 2).

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[16 18 32 48 64] is associated with increased risk of pulmonary complications including bronchopulmonary dysplasia,[29 93] necrotising enterocolitis,[6] and neurological injury including cystic periventricular leukomalacia and cerebral palsy.[3 38 56 57 90–92] 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.[68]

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.[68] 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,[60] 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*,[73] 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.[77]

Subset of acute chorioamnionitis with peripheral microabscesses of the umbilical cord

As shown by Kaplan (this issue),[96] 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

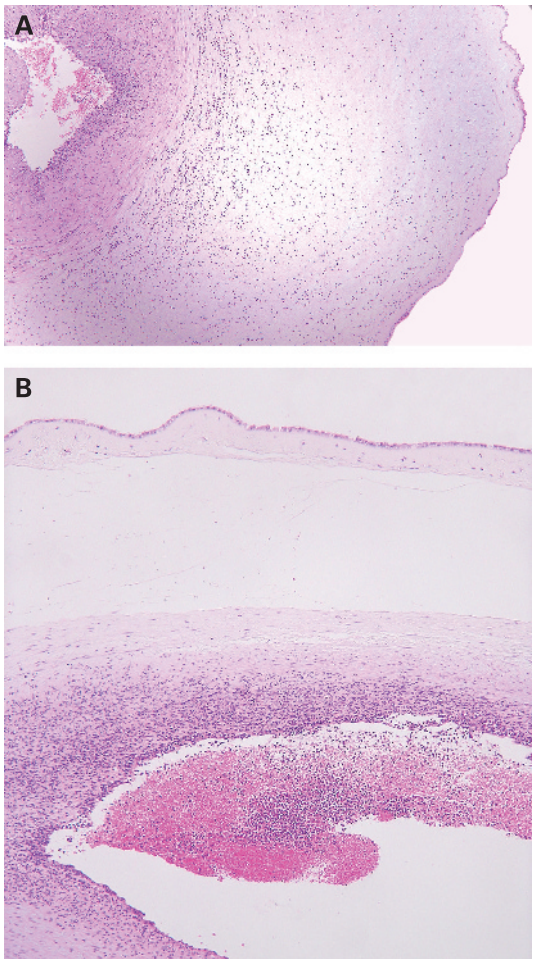

Figure 4 Fetal inflammatory response, grade 2. (A) Intense inflammation of an umbilical artery along with necrotising funisitis (fetal stage 3). (B) Grade 2 response in a chorionic plate vessel.

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.[66] 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*,[47 66] but, since so few placentas 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.[47] It was first proposed as a diagnostic entity by Ohyama *et al*[63] in their report of 90 preterm placentas 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.[47] The differential diagnosis includes chronic, predominantly lymphocytic, chorionitis which is generally focal and associated with villitis of unknown aetiology. (See non-microbial causes of preterm birth, below.)

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).[24] 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 placentitis, and haematogenous spread of the organism predominates.[24] 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 tularaemia 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

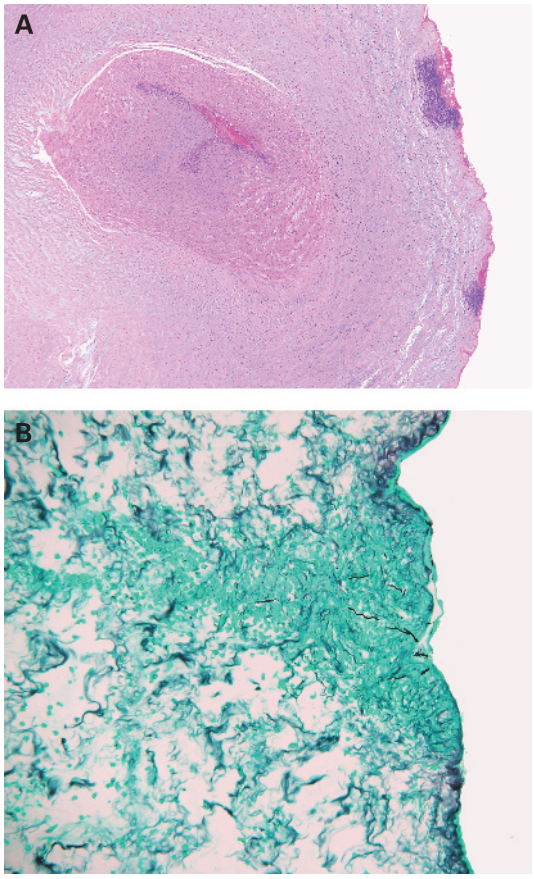

Figure 5 Peripheral funisitis. (A) There are two peripheral microabscesses on this cord section. Care should be taken when subsequent sections are cut from the paraffin block for special stains, since these lesions may be "cut through" and diagnostic foci lost. (B) Gomori methenamine silver stains confirm the presence of *Candida pseudohyphae*.

infection. *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.[47] 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 (**T**oxoplasmosis, **O**thers, **R**ubella virus, **C**ytomegalovirus, and **H**erpes simplex virus); all of these result in fetal onset of growth restriction, hepatosplenomegaly, cytopaenias, 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%)[70]; 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.[26]

CMV placentitis

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[24] (fig 8A–E). The author recommends immunostaining

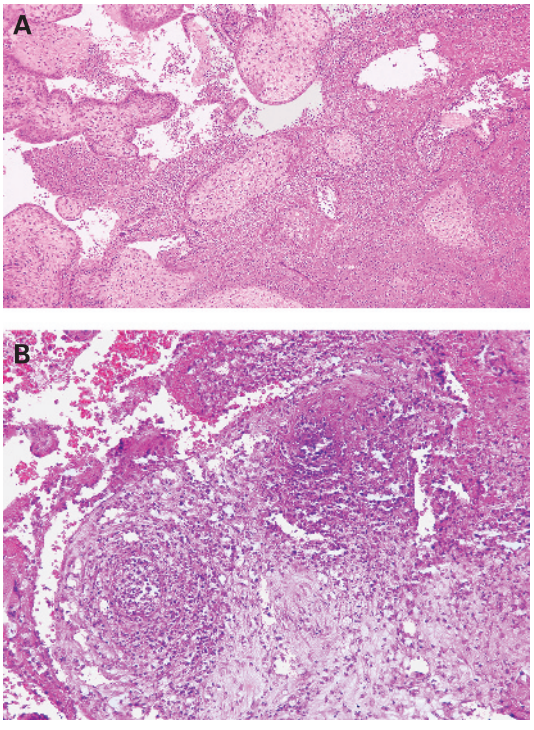

Figure 6 Acute villitis due to *Listeria. monocytogenes*. (A) Low power photomicrograph showing an intense acute intervillositis and a focus of acute, destructive villitis. Such confluent regions of inflammation and necrosis may be grossly detectable as abscesses on cut surfaces of the placenta. Such cases also show severe histological acute chorioamnionitis. (Material generously provided by Dr B Waters, Fletcher Allen Health Care, Burlington, Vermont, USA.) (B) Higher power image showing severe acute inflammatory response in the chorionic villi from a case of extreme preterm birth. Tissue Gram stains showed Gram positive bacilli.

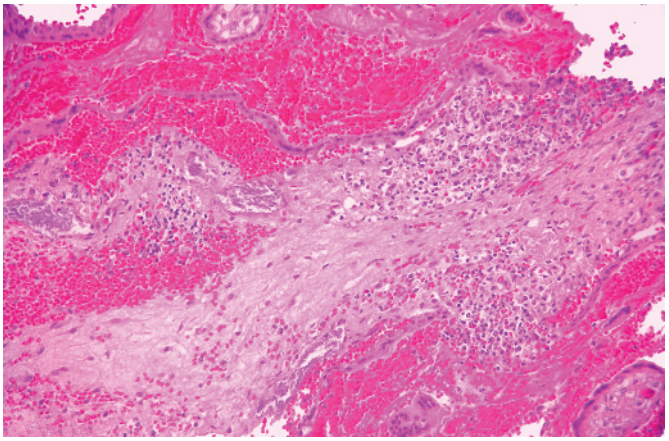

Figure 7 Acute villitis with fetal sepsis. Sections from a case of preterm PROM and neonatal sepsis due to *Escherichia coli* show neutrophils in the chorionic villous capillaries and villous stroma. Vascular lumina on the left aspect of the image show aggregates of bacteria due to bacterial overgrowth.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

four transmural sections, particularly if sclerosis is prominent. Use of PCR for CMV early and late gene anitigen gp 64 has also been reported.[61] Lymphoplasmacytie 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 intervillositis, with trophoblastic multinucleation and viral cytopathy. The villitis/intervillositis 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

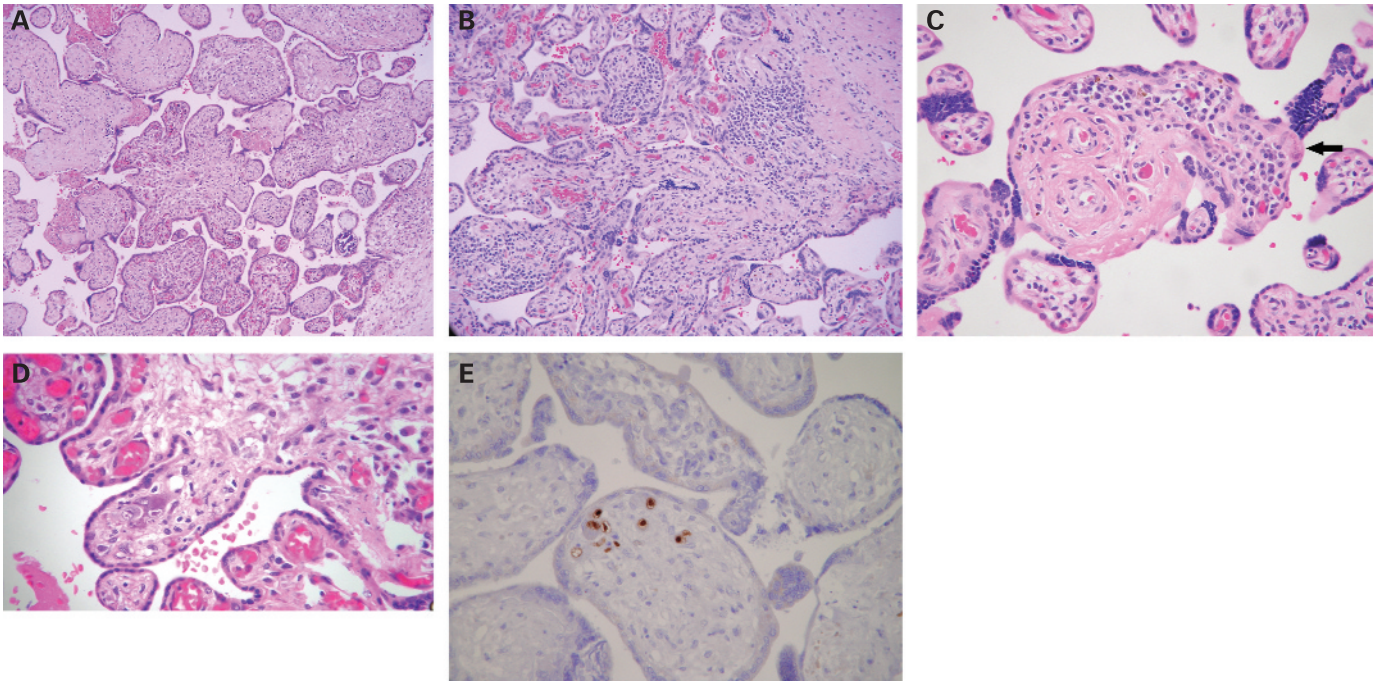

Figure 8 Chronic villitis due to cytomegalovirus. (A) Low power image showing chorionic villous dysmaturity, patchy villous sclerosis, and chronic villitis. (B) Higher magnification confirms the presence of stromal lymphoplasmacytic infiltrate. (C) Chorionic villus shows lymphoplasmacytic villitis, iron 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.

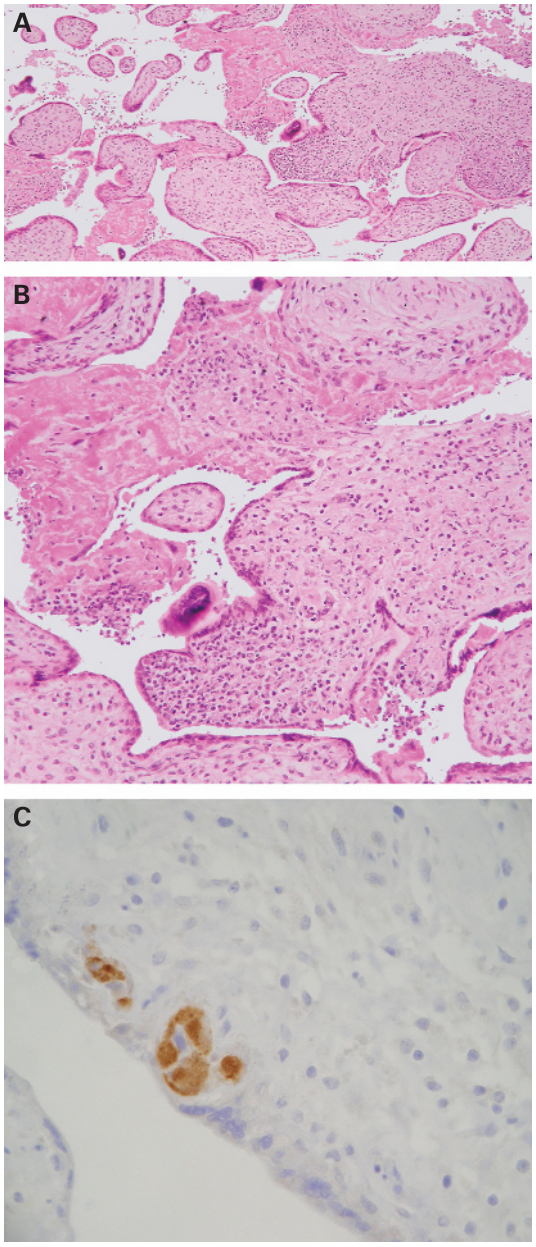

Figure 9 Chronic villitis due to herpes simplex virus. (A) Low power photomicrograph shows aggregates of fibrin and inflammation, and chronic villitis with villous destruction. (B) Higher magnification reveals lymphoplasmacytic infiltrate and villous necrosis that merges with intervillous fibrin and inflammation. (C) Immunoperoxidase stain for HSV is positive and reveals multinucleation.

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 deciduitis, 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[41] (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

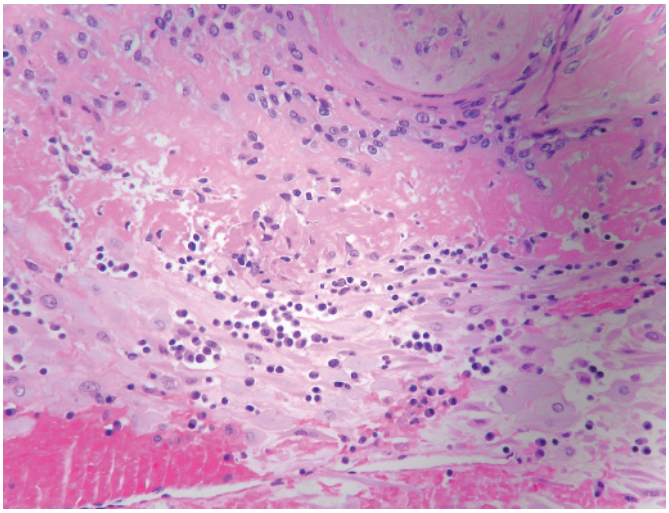

Figure 10 Chronic deciduitis, isolated to the decidua basalis. The decidua shows lymphoplasmacytic deciduitis without basal chronic villitis. Villitis was not identified elsewhere in several sections of this placenta from a spontaneous preterm birth. The mother had a history of a prior preterm birth.

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.[69] In a recent study of endometrial microbial colonisation and chronic endometritis in women who were 3 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.[7] 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.[19] 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[12 31 37] and uterine anomalies.[37]

Associated placental pathology

Extravasated blood is a biochemical irritant. Clinical findings suggest that pathological findings of chronic, thin,

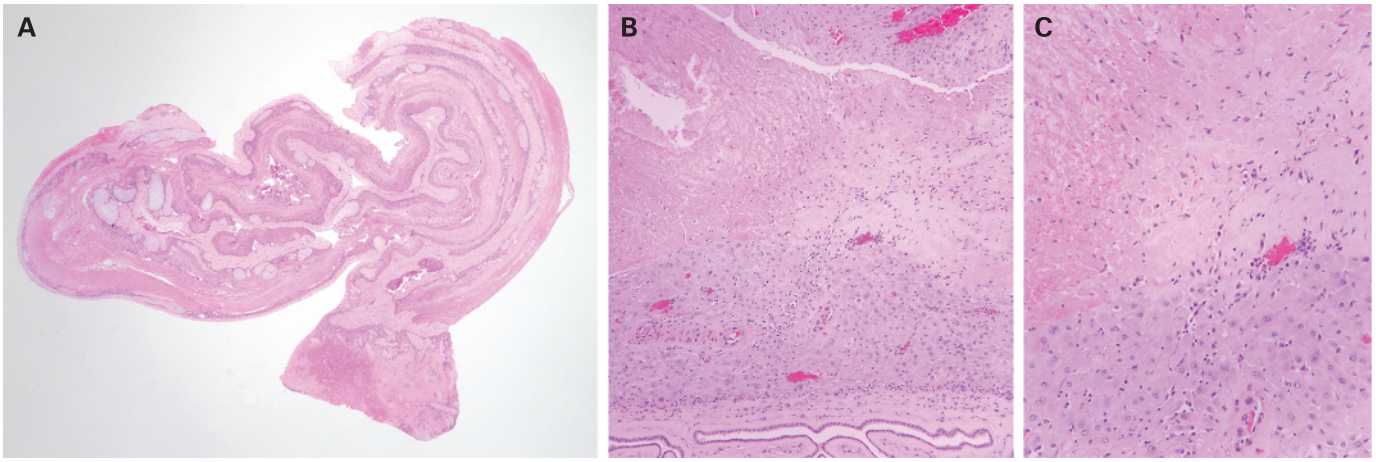

Figure 11 (A) Chronic retromembranous haemorrhage, showing recent and chronic features in a case from spontaneous preterm birth with preterm labour at 33 weeks of gestation. There was no chorioamnionitis or villitis. The woman had a history of hypertension (blood pressure 145–150/90 mm Hg), but no thrombophilia, autoimmune disease or trauma. (B) Higher power shows that the haemorrhage dissects in a plane within the decidua capsularis, and (C) shows the presence of hemosiderin-laden macrophages.

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.[84] 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*.[86] 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,[43] 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 trophoblast cell line models.[34 40] Notably TNFα in cervical secretions is of one of many potential cytokines that has been identified as a marker of preterm labour in women *without* risk factors of hypertension. In addition, the ratio of TNFα concentration to that of its soluble TNFα-receptor has been found to be higher in amniotic fluid in cases of preterm labour with preterm delivery versus preterm labour with term delivery.[51] Furthermore, the bioavailability of TNFα in amniotic fluid from blacks is higher than that of whites.[54] As referenced above, blacks are also at increased risk for early preterm and recurrent preterm birth.[21] TNFα also increases production of other inflammatory cytokines, matrix metalloproteinases involved in amnion degradation, and mediators of increased uterine tonicity (ie, prostaglandin production by amnion, decidua and myometrium),[36 80] and may play a role in cervical ripening.[80] In addition, TNFα administration can induce parturition in animals,[80] and anti-TNFα administration to pregnant mice has been shown to significantly reduce rates of PTL and stillbirth.[36] 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,[21 54 65] 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.[22 53 55 82] Esplin *et al* identified 56 different differentially expressed human myometrial transcriptomes associated with term labour and confirmed four as specifically up-regulated.[22] 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).[23] 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,[27] 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

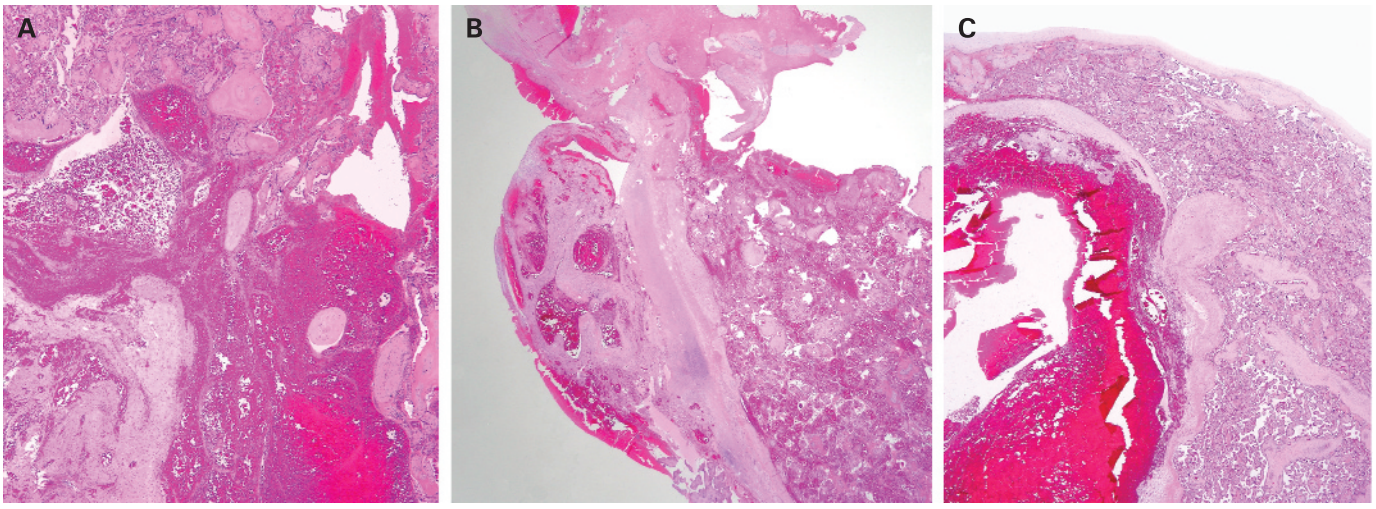

Figure 12 Acute marginal hematoma (MH). (A) The lateral placental margin (delimited by a layer of decidua at the placental margin) is disrupted by acute haemorrhage that dissects into the chorionic villous parenchyma. (B) Example of large maternal venous vessels normally present at the lateral placental margin. The occurrence of MH is attributed to bleeding from these veins. (This image also shows acute villous congestion and intravillous 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.

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.[69] 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

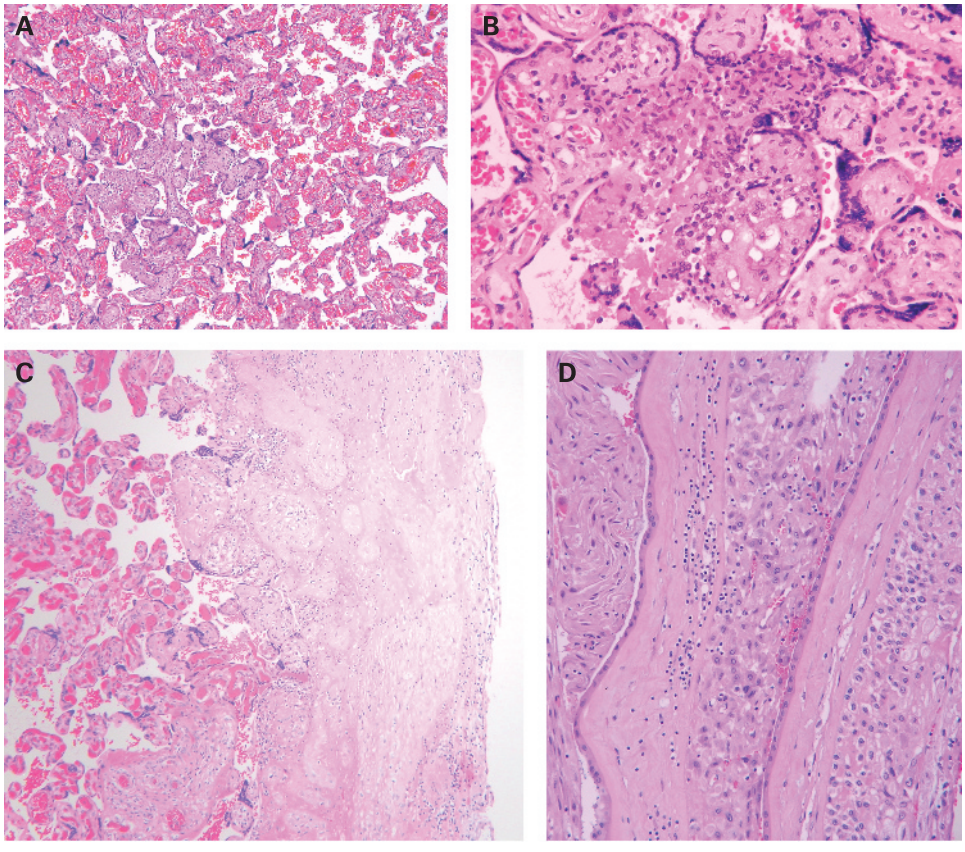

Figure 13 Chronic villitis of unknown aetiology (VUA). (A) VUA is best identified at low power scan. It is chronic lymphohistiocytic villitis that affects only a few villi and less than 5% of the total villi examined. Several left-central terminal villi are affected in this microscopic field. (B) High 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.

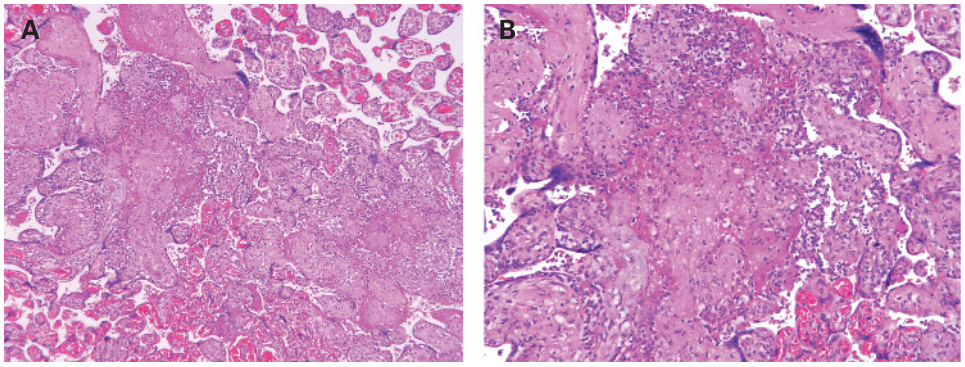

Figure 14 Diffuse chronic villitis. (A) Diffuse villitis of unknown aetiology is characterised by involvement of more than 5% of the villi. This image shows relatively extensive involvement and destruction with patchy intervillositis. Villi appear matted together. (B) Higher power further reveals the villous lymphohistiocytic inflammation of some villi with the sparing of others.

circumvallation.[1 85 88] It is important to note that the clinically used term "subchorionic haemorrhage", is different from subchorionic *thrombohematoma*, also called Breus mole, which refers to a central, nodular protuberance on the fetal surface of the placenta, from thrombohematoma formation in the *maternal space*. Harris *et al* noted that over half of the placentas delivered of women with idiopathic PTL without antepartum bleeding showed marginal adherent clot, with fibrin deposition and lamination, polymorphonuclear infiltration and marginal decidual necrosis: these are gross and histological criteria of acute antepartum peripheral placental separation.[33] These 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 accumulation (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 parenchyma 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 disorders 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 (morphological feature of syncytiotrophoblast–endothelial cell basement membranous apposition) characteristic of 32 or more weeks of gestational development. Therefore, it must be underscored that the diagnosis should be made with caution in preterm placentas,[70] and "restricted" to cases of 32–36 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

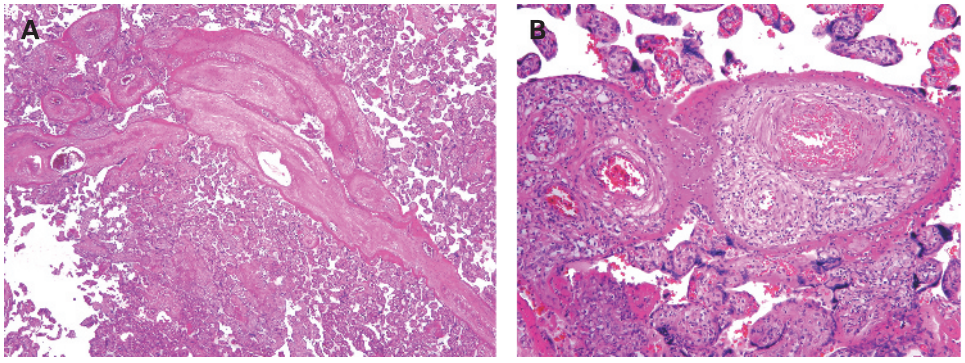

Figure 15 Chronic villitis with obliterative vasculopathy. (A) Low power reveals the presence of thrombosis in stem villi and involuting and sclerotic distal villi, in addition to prominent chronic villitis (B) Villitis, and vasculitis and vascular obliteration in the stem villi. Stem villous vessels show disruption and erythrocyte extravasation in the wall. Inflamed and sclerotic villi are present in the lower aspect of the image.

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).[42] 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.[69 70] However, there is a long recognised strong risk correlation between VUA and idiopathic IUGR.[2 4 5 10 11 46 69 70 81] 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.[69–71] VUA has also been linked to unexplained (non-infectious spontaneous) preterm birth and perinatal asphyxia.[10] 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[11 69 70] (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[75] with a CD4:CD8 ratio of 0.1–0.5% and Hofbauer cells of fetal origin.[44 59] Fetal Hofbauer cells are activated with up-regulation of major histocompatibility antigens and have a high rate of proliferation.[44] The observations of activation and hyperplasia of fetal Hofbauer cells[44] 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.[44 69 70] 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.[69–71] Not coincidentally, VUA is also more frequent in patients of high gravidity and in pregnancies affected by maternal autoimmune or alloimmune diseases.[69–71] Obesity and diabetes mellitus may contribute to placentomegaly and greater trophoblast availability to maternal exposure and sensitisation.[11 70] 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[8] are of maternal origin. Moreover, maternal cells may persist in the peripheral blood of children for up to three decades.[58]

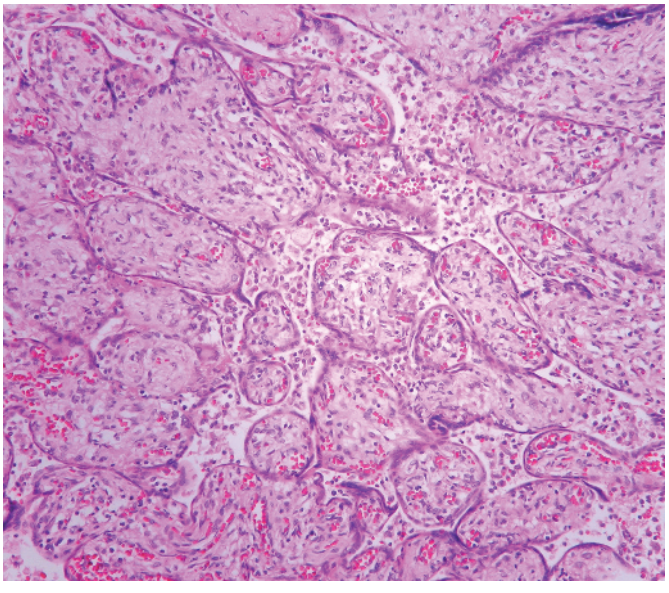

Figure 16 Massive chronic intervillositis. Prominent aggregates of lymphocytes and monocytes are seen in the maternal space. In contrast to villitis of unknown aetiology, there is no essentially no villitis.

Massive chronic intervillosits

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.[69] It is likely an alloimmune phenomenon, and it is unclear if it is a variant of VUA.[69 78]

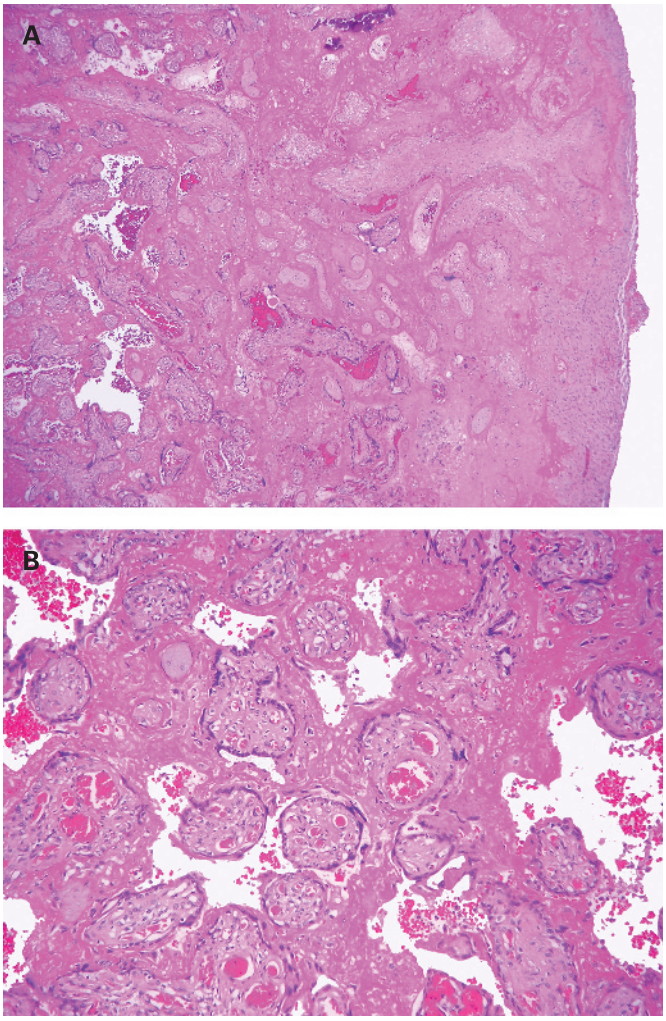

Figure 17 Maternal floor infarction. (A) Maternal floor infarction is characterised by dense perivillous fibrinoid deposition in the basal maternal space with associated involution and atrophy of the chorionic villi. This placental image is from a 26 week delivery of a growth restricted infant with non-reassuring 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.

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).[9 24 68 74] 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.[15 20 24] 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%)[24]; when of early onset, there is an associated increased risk of recurrence and severity in subsequent pregnancies.[25] 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.[24]

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 intervillositis 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.

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

1. **Abu-Yousef MM,** Bleicher JJ, Williamson RA, *et al*. Subchorionic hemorrhage: sonographic diagnosis and clinical significance. *AJR* 1987;**149**:737–40.
2. **Agapitos E,** Papadopoulou C, Kavantzas N, *et al*. The contribution of pathological examination of the placenta in the investigation of the causes of foetal mortality. *Archives d'anatomie et de cytologie pathologiques* 1996;**44**:5–11.
3. **Alexander JM,** Gilstrap LC, Cox SM, *et al*. Clinical chorioamnionitis and the prognosis for very low birth weight infants. *Obstet Gynecol* 1998;**91**:725–9.
4. **Althabe O,** Labarrere C. Chronic villitis of unknown aetiology and intrauterine growth-retarded infants of normal and low ponderal index. *Placenta* 1985;**6**:369–73.
5. **Altshuler G,** Russell P, Ermocilla R. The placental pathology of small-for-gestational age infants. *Am J Obstet Gynecol* 1975;**121**:351–9.
6. **Andrews WW,** Goldenberg RL, Faye-Petersen O, *et al*. The Alabama Preterm Birth study: polymorphonuclear and mononuclear cell placental infiltrations, other markers of inflammation, and outcomes in 23- to 32-week preterm newborn infants. *Am J Obstet Gynecol* 2006;**195**:803–8.
7. **Andrews WW,** Goldenberg RL, Hauth JC, *et al*. Endometrial microbial colonization and plasma cell endometritis after spontaneous or indicated preterm versus term delivery. *Am J Obstet Gynecol* 2005;**193**:739–45.
8. **Artlett CM,** Miller FW, Rider LG. Persistent maternally derived peripheral microchimerism is associated with the juvenile idiopathic inflammatory myopathies. *Rheumatology (Oxford)* 2001;**40**:1279–84.
9. **Benirschke KKP,** Baergen RN. *Pathology of the human placenta*, 5th edn. New York, NY: Springer, 2006:682–761.
10. **Bjoro K Jr,** Myhre E. The role of chronic non-specific inflammatory lesions of the placenta in intra-uterine growth retardation. *Acta Pathol Microbiol Immunol Scand* 1984;**92**:133–7.
11. **Boog G.** Chronic villitis of unknown etiology. *Eur J Obstet Gynecol Reprod Biol* 2008;**136**:9–15.
12. **Buhimschi CS,** Rosenberg VA, Dulay AT, *et al*. Multidimensional system biology: genetic markers and proteomic biomarkers of adverse pregnancy outcome in preterm birth. *Am J Perinatol* 2008;**25**:175–87.
13. **Chaiworapongsa T,** Erez O, Kusanovic JP, *et al*. Amniotic fluid heat shock protein 70 concentration in histologic chorioamnionitis, term and preterm parturition. *J Matern Fetal Neonatal Med* 2008;**21**:449–61.
14. **Christiaens I,** Zaragoza DB, Guilbert L, *et al*. Inflammatory processes in preterm and term parturition. *J Reprod Immunol*. In press.
15. **Dahms BB,** Boyd T, Redline RW. Severe perinatal liver disease associated with fetal thrombotic vasculopathy. *Pediatr Dev Pathol* 2002;**5**:80–5.
16. **Dammann O,** Allred EN, Leviton A, *et al*. Fetal vasculitis in preterm newborns: interrelationships, modifiers, and antecedents. *Placenta* 2004;**25**:788–96.
17. **DeFranco E,** Teramo K, Muglia L. Genetic influences on preterm birth. *Semin Reprod Med* 2007;**25**:40–51.
18. **Dollner H,** Vatten L, Halgunset J, *et al*. Histologic chorioamnionitis and umbilical serum levels of pro-inflammatory cytokines and cytokine inhibitors. *BJOG* 2002;**109**:534–9.
19. **Edmondson N,** Bocking A, Machin G, *et al*. The prevalence of chronic deciduitis in cases of preterm labour without clinical chorioamnionitis. *Pediatr Dev Pathol*. In press.
20. **Ernst LM,** Grossman AB, Ruchelli ED. Familial perinatal liver disease and fetal thrombotic vasculopathy. *Pediatr Dev Pathol* 2008;**11**:160–3.
21. **Esplin MS.** Preterm birth: a review of genetic factors and future directions for genetic study. *Obstet Gynecol Surv* 2006;**61**:800–6.
22. **Esplin MS,** Fausett MB, Peltier MR, *et al*. The use of cDNA microarray to identify differentially expressed labor-associated genes within the human myometrium during labor. *Am J Obstet Gynecol* 2005;**193**:404–13.
23. **Esplin MS,** Peltier MR, Hamblin S, *et al*. Monocyte chemotactic protein-1 expression is increased in human gestational tissues during term and preterm labor. *Placenta* 2005;**26**:661–71.
24. **Faye-Petersen OM,** Heller DS, Joshi VV. *Handbook of placental pathology*. Oxford: Taylor and Francis, 2006.
25. **Faye-Petersen OM,** Reilly SD. Demystifying the pathologic diagnoses of villitis and fetal thrombotic vasculopathy. *NeoReviews* 2008;**9**:e399–410.
26. **Fowler KB,** Stagno S, Pass RF, *et al*. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med* 1992;**326**:663–7.
27. **Fox HSN,** Sebire NJ. *Pathology of the placenta. Major problems in pathology*, 3rd edn. Philadelphia, PA: Saunders Elsevier, 2007:123–337.
28. **Goldenberg RL,** Andrews WW, Faye-Petersen OM, *et al*. The Alabama Preterm Birth Study: corticosteroids and neonatal outcomes in 23- to 32-week newborns with various markers of intrauterine infection. *Am J Obstet Gynecol* 2006;**195**:1020–4.
29. **Goldenberg RL,** Andrews WW, Goepfert AR, *et al*. The Alabama Preterm Birth Study: umbilical cord blood Ureaplasma urealyticum and Mycoplasma hominis cultures in very preterm newborn infants. *Am J Obstet Gynecol* 2008;**198**:e41–5.
30. **Goldenberg RL,** Culhane JF. Low birth weight in the United States. *Am J Clin Nutr* 2007;**85**:584S–90S.
31. **Goldenberg RL,** Culhane JF, Iams JD, *et al*. Epidemiology and causes of preterm birth. *Lancet* 2008;**371**:75–84.
32. **Gomez R,** Romero R, Ghezzi F, *et al*. The fetal inflammatory response syndrome. *Am J Obstet Gynecol* 1998;**179**:194–202.
33. **Harris BA Jr,** Gore H, Flowers CE Jr. Peripheral placental separation: a possible relationship to premature labor. *Obstet Gynecol* 1985;**66**:774–8.
34. **Harris LK,** Keogh RJ, Wareing M, *et al*. BeWo cells stimulate smooth muscle cell apoptosis and elastin breakdown in a model of spiral artery transformation. *Hum Reprod* 2007;**22**:2834–41.
35. **Hecht JL,** Onderdonk A, Delaney M, *et al*. Characterization of chorioamnionitis in 2nd-trimester C-section placentas and correlation with microorganism recovery from subamniotic tissues. *Pediatr Dev Pathol* 2008;**11**:15–22.
36. **Holmgren C,** Esplin MS, Hamblin S, *et al*. Evaluation of the use of anti-TNF-alpha in an LPS-induced murine model. *J Reprod Immunol* 2008;**78**:134–9.
37. **Iams JD,** Romero R, Culhane JF, *et al*. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet* 2008;**371**:164–75.
38. **Jacobsson B,** Hagberg G. Antenatal risk factors for cerebral palsy. *Best Pract Res Clin Obstet Gynaecol* 2004;**18**:425–36.
39. **Kapur P,** Rakheja D, Gomez AM, *et al*. Characterization of inflammation in syphilitic villitis and in villitis of unknown etiology. *Pediatr Dev Pathol* 2004;**7**:453–8.
40. **Keogh RJ,** Harris LK, Freeman A, *et al*. Fetal-derived trophoblast use the apoptotic cytokine tumor necrosis factor-alpha-related apoptosis-inducing ligand to induce smooth muscle cell death. *Circulation Res* 2007;**100**:834–41.
41. **Khong TY,** Bendon RW, Qureshi F, *et al*. Chronic deciduitis in the placental basal plate: definition and interobserver reliability. *Hum Pathol* 2000;**31**:292–5.
42. **Khong TY,** Staples A, Moore L, *et al*. Observer reliability in assessing villitis of unknown aetiology. *J Clin Pathol* 1993;**46**:208–10.
43. **Kilani RT,** Mackova M, Davidge ST, *et al*. Endogenous tumor necrosis factor alpha mediates enhanced apoptosis of cultured villous trophoblasts from intrauterine growth-restricted placentae. *Reproduction* 2007;**133**:257–64.
44. **Kim JS,** Romero R, Kim MR, *et al*. Involvement of Hofbauer cells and maternal T cells in villitis of unknown aetiology. *Histopathology* 2008;**52**:457–64.
45. **Kim KW,** Romero R, Park HS, *et al*. A rapid matrix metalloproteinase-8 bedside test for the detection of intraamniotic inflammation in women with preterm premature rupture of membranes. *Am J Obstet Gynecol* 2007;**197**:e291–5.
46. **Knox WF,** Fox H. Villitis of unknown aetiology: its incidence and significance in placentae from a British population. *Placenta* 1984;**5**:395–402.
47. **Kraus FT,** Redline RW, Gersell DJ, *et al*. *Placental pathology. Atlas of nontumor pathology*. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology, 2004:75–115.
48. **Lee SE,** Romero R, Jung H, *et al*. The intensity of the fetal inflammatory response in intraamniotic inflammation with and without microbial invasion of the amniotic cavity. *Am J Obstet Gynecol* 2007;**197**: e291–6.
49. **Liu H,** Redline RW, Han YW. Fusobacterium nucleatum induces fetal death in mice via stimulation of TLR4-mediated placental inflammatory response. *J Immunol* 2007;**179**:2501–8.
50. **Manau C,** Echeverria A, Agueda A, *et al*. Periodontal disease definition may determine the association between periodontitis and pregnancy outcomes. *J Clin Periodontol* 2008;**35**:385–97.
51. **Maymon E,** Ghezzi F, Edwin SS, *et al*. The tumor necrosis factor alpha and its soluble receptor profile in term and preterm parturition. *Am J Obstet Gynecol* 1999;**181**:1142–8.
52. **McParland PJG,** Taylor D. Preterm labour and prematurity. *Curr Obstet Gynaecol* 2004;**14**:309–19.

53. **Menon R,** Camargo MC, Thorsen P, *et al*. Amniotic fluid interleukin-6 increase is an indicator of spontaneous preterm birth in white but not black Americans. *Am J Obstet Gynecol* 2008;**198**:e71–7.
54. **Menon R,** Thorsen P, Vogel I, *et al*. Racial disparity in amniotic fluid concentrations of tumor necrosis factor (TNF)-alpha and soluble TNF receptors in spontaneous preterm birth. *Am J Obstet Gynecol* 2008;**198**:e531–10.
55. **Menon R,** Williams SM, Fortunato SJ. Amniotic fluid interleukin-1beta and interleukin-8 concentrations: racial disparity in preterm birth. *Reprod Sci* 2007;**14**:253–9.
56. **Minagawa K,** Tsuji Y, Ueda H, *et al*. Possible correlation between high levels of IL-18 in the cord blood of pre-term infants and neonatal development of periventricular leukomalacia and cerebral palsy. *Cytokine* 2002;**17**:164–70.
57. **Moon JB,** Kim JC, Yoon BH, *et al*. Amniotic fluid matrix metalloproteinase-8 and the development of cerebral palsy. *J Perinat Med* 2002;**30**:301–6.
58. **Muraji T,** Hosaka N, Irie N, *et al*. Maternal microchimerism in underlying pathogenesis of biliary atresia: quantification and phenotypes of maternal cells in the liver. *Pediatrics* 2008;**121**:517–21.
59. **Myerson D,** Parkin RK, Benirschke K, *et al*. The pathogenesis of villitis of unknown etiology: analysis with a new conjoint immunohistochemistry-in situ hybridization procedure to identify specific maternal and fetal cells. *Pediatr Dev Pathol* 2006;**9**:257–65.
60. **Naeye RL,** Maisels MJ, Lorenz RP, *et al*. The clinical significance of placental villous edema. *Pediatrics* 1983;**71**:588–94.
61. **Nakamura Y,** Sakuma S, Ohta Y, *et al*. Detection of the human cytomegalovirus gene in placental chronic villitis by polymerase chain reaction. *Hum Pathol* 1994;**25**:815–8.
62. **Norwitz ER,** Robinson JN, Challis JR. The control of labor. *N Engl J Med* 1999;**341**:660–6.
63. **Ohyama M,** Itani Y, Yamanaka M, *et al*. Re-evaluation of chorioamnionitis and funisitis with a special reference to subacute chorioamnionitis. *Hum Pathol* 2002;**33**:183–90.
64. **Pacora P,** Chaiworapongsa T, Maymon E, *et al*. Funisitis and chorionic vasculitis: the histological counterpart of the fetal inflammatory response syndrome. *J Matern Fetal Neonatal Med* 2002;**11**:18–25.
65. **Plunkett J,** Muglia LJ. Genetic contributions to preterm birth: implications from epidemiological and genetic association studies. *Ann Med* 2008;**40**:167–95.
66. **Qureshi F,** Jacques SM, Bendon RW, *et al*. Candida funisitis: a clinicopathologic study of 32 cases. *Pediatr Dev Pathol* 1998;**1**:118–24.
67. **Redline RW.** Infections and other inflammatory conditions. *Semin Diagn Pathol* 2007;**24**:5–13.
68. **Redline RW.** Inflammatory responses in the placenta and umbilical cord. *Semin Fetal Neonatal Med* 2006;**11**:296–301.
69. **Redline RW.** Placental pathology: a systematic approach with clinical correlations. *Placenta* 2008;**29**(suppl A):S86–91.
70. **Redline RW.** Villitis of unknown etiology: noninfectious chronic villitis in the placenta. *Hum Pathol* 2007;**38**:1439–46.
71. **Redline RW,** Abramowsky CR. Clinical and pathologic aspects of recurrent placental villitis. *Hum Pathol* 1985;**16**:727–31.
72. **Redline RW,** Faye-Petersen O, Heller D, *et al*. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol* 2003;**6**:435–48.
73. **Redline RW,** Minich N, Taylor HG, *et al*. Placental lesions as predictors of cerebral palsy and abnormal neurocognitive function at school age in extremely low birth weight infants (<1 kg). *Pediatr Dev Pathol* 2007;**10**:282–92.
74. **Redline RW,** Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. *Hum Pathol* 1995;**26**:80–5.
75. **Redline RW,** Patterson P. Villitis of unknown etiology is associated with major infiltration of fetal tissue by maternal inflammatory cells. *Am J Pathol* 1993;**143**:473–9.
76. **Redline RW,** Wilson-Costello D, Borawski E, *et al*. The relationship between placental and other perinatal risk factors for neurologic impairment in very low birth weight children. *Pediatr Res* 2000;**47**:721–6.
77. **Reilly SD,** Faye-Petersen OM. Chorioamnionitis and funisitis: their implications for the neonate. *NeoReviews* 2008;**9**:e411–7.
78. **Roberts DJ,** Post MD. The placenta in pre-eclampsia and intrauterine growth restriction. *J Clin Pathol* 2008;**61**:1254–60.
79. **Romero R,** Espinoza J, Goncalves LF, *et al*. The role of inflammation and infection in preterm birth. *Semin Reprod Med* 2007;**25**:21–39.
80. **Romero R,** Gotsch F, Pineles B, *et al*. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. *Nutr Rev* 2007;**65**:S194–202.
81. **Russell P.** Inflammatory lesions of the human placenta. III. The histopathology of villitis of unknown aetiology. *Placenta* 1980;**1**:227–44.
82. **Sadowsky DW,** Adams KM, Gravett MG, *et al*. Preterm labor is induced by intraamniotic infusions of interleukin-1beta and tumor necrosis factor-alpha but not by interleukin-6 or interleukin-8 in a nonhuman primate model. *Am J Obstet Gynecol* 2006;**195**:1578–89.
83. **Saigal S,** Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008;**371**:261–9.
84. **Salafia CM,** Lopez-Zeno JA, Sherer DM, *et al*. Histologic evidence of old intrauterine bleeding is more frequent in prematurity. *Am J Obstet Gynecol* 1995;**173**:1065–70.
85. **Stabile I,** Campbell S, Grudzinskas JG. Threatened miscarriage and intrauterine hematomas. Sonographic and biochemical studies. *J Ultrasound Med* 1989;**8**:289–92.
86. **Stanek J,** Al-Ahmadie HA. Laminar necrosis of placental membranes: a histologic sign of uteroplacental hypoxia. *Pediatr Dev Pathol* 2005;**8**:34–42.
87. **Steel JH,** Malatos S, Kennea N, *et al*. Bacteria and inflammatory cells in fetal membranes do not always cause preterm labor. *Pediatr Res* 2005;**57**:404–11.
88. **Takeda S,** Baba K, Kojima T, *et al*. Ultrasonographic monitoring of the placenta in patients with bleeding during the first and second trimesters. *Asia-Oceania J Obstet Gynecol* 1990;**16**:211–8.
89. **Verma RP,** Kaplan CG, Southerton K, *et al*. Placental histopathology in the extremely low birth weight infants. *Fetal Pediatr Pathol* 2008;**27**:53–61.
90. **Wharton KN,** Pinar H, Stonestreet BS, *et al*. Severe umbilical cord inflammation—a predictor of periventricular leukomalacia in very low birth weight infants. *Early Hum Dev* 2004;**77**:77–87.
91. **Wu YW,** Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. *JAMA* 2000;**284**:1417–24.
92. **Yoon BH,** Park CW, Chaiworapongsa T. Intrauterine infection and the development of cerebral palsy. *BJOG* 2003;**110**(suppl 20):124–7.
93. **Yoon BH,** Romero R, Jun JK, *et al*. Amniotic fluid cytokines (interleukin-6, tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-8) and the risk for the development of bronchopulmonary dysplasia. *Am J Obstet Gynecol* 1997;**177**:825–30.
94. **Yoon BH,** Romero R, Moon JB, *et al*. Clinical significance of intra-amniotic inflammation in patients with preterm labor and intact membranes. *Am J Obstet Gynecol* 2001;**185**:1130–6.
95. **Yoon BH,** Romero R, Park JS, *et al*. The relationship among inflammatory lesions of the umbilical cord (funisitis), umbilical cord plasma interleukin 6 concentration, amniotic fluid infection, and neonatal sepsis. *Am J Obstet Gynecol* 2000;**183**:1124–9.
96. **Kaplan C.** Gross pathology of the placenta—weight, shape, size, colour, etc. *J Clin Pathol* 2008;**61**:1285–95.