DOI: 10.1111/tog.12555
The Obstetrician & Gynaecologist
http://onlinetog.org
2019;21:135–42

Review

Placental histopathological abnormalities and poor perinatal outcomes

Lakshmi Thirumalaikumar FRCOG,[a,*] **Kalaivani Ramalingam** FRCOG,[b] **Tamas Marton** MD PhD[c]

[a]Consultant Obstetrician, Department of O&G, Worcester Royal Hospital, Worcester WR5 1DD, UK
[b]Consultant Obstetrician and Gynaecologist, Department of O&G, Apollo Hospitals, Chennai, India
[c]Consultant Perinatal Pathologist, Department of Perinatal pathology, Birmingham Women's Hospital, Birmingham B15 2TG, UK
*Correspondence: Lakshmi Thirumalaikumar. Email: lakshmi.thirumalaikumar@nhs.net

Accepted on 26 July 2018. Published Online 14 March 2019.

Key content
- Examination of the placenta is important and must be correlated with the clinical conditions.
- Placental histology can yield valuable information in cases of adverse perinatal outcome.
- Information obtained from the placenta is vital to formulate an appropriate plan of care in subsequent pregnancy.

Learning objectives
- To understand the correlation between placental histology and pregnancy outcome.
- To identify the clinical conditions that will benefit from placental histology.
- To understand the process of storing the placenta for different examination techniques.

Ethical issues
- Should the placenta be sent for histology in all cases of growth restriction and stillbirth?
- Is it cost effective to undertake universal placental histology?

Keywords: histology / placenta / pregnancy outcome

Please cite this paper as: Thirumalaikumar L, Ramalingam K, Marton T. Placental histopathological abnormalities and poor perinatal outcomes. *The Obstetrician & Gynaecologist*. 2019;21:135–42. https://doi.org/10.1111/tog.12555

Introduction

The placenta supports the development and growth of the fetus through specialised functions including transport of respiratory gases; carbohydrate, amino acid and lipid metabolism; transfer of minerals and vitamins; and production of growth factors and hormones. The placental barrier also protects the fetus against bacterial and viral infections.[1] A review of the recent literature provides evidence that lesions in the placenta can affect its function, leading to significant morbidity for the mother and her fetus. These lesions may be associated with maternal vascular underperfusion, infection and fetal thrombosis.[2] Placental villous structure abnormalities correlate with the time of onset of fetal growth restriction, helping to differentiate between early and late onset. Placental histology is vital in cases of fetal growth restriction as it helps to define the cause and predict the risk of recurrence.[3]

This article aims to address the indications for undertaking a placental histology assessment, the methods of storing and sending the placenta for analysis and normal placental development. We discuss placental histology findings in conditions with adverse outcomes, such as fetal growth restriction and stillbirth. The macroscopic variations of the placenta, placental neoplasms and placental changes in multiple pregnancy are not within the scope of this article and hence are not addressed.

Guidance on indications for, and the process of, placental evaluation

A recent update from the Royal College of Pathologists[4] on the tissue pathway for histological examination of the placenta provides guidance on the indications and minimum standards for placental examinations. The indications for placental evaluation, as outlined in the pathway, are summarised in Table 1. It is good practice to request placental histology when there is unexpected admission of the baby to the neonatal unit. This may confirm evidence of subclinical chorioamnionitis or other placental features that led to the unexpected outcome.

The extent of the examination depends on the clinical information provided, along with the placental evaluation.[3] The pathway describes the basic relevant clinical information needed to assess the placenta and outlines a simple placental referral proforma. This proforma is in use in hospitals in the

Table 1. Indications for placental histology as recommended by the Royal College of Pathologists

Placental examination is ESSENTIAL	Placental examination is DESIRABLE	Placental examination is NOT indicated
Stillbirth (antepartum or intrapartum)	Prematurity (30^{+0}–36^{+6}/40)	Cholestasis of pregnancy
Late miscarriage	Placental abruption	Pruritis of pregnancy
Severe fetal distress requiring admission to neaonatal unit	Fetal congenital malformation	Hepatitis B, HIV, etc.
	Rhesus isoimmunisation	Other maternal disease with normal pregnancy outcome
Prematurity (<30^{+0}/40)	Morbidly adherent placenta	Placenta praevia
Fetal growth restriction (birthweight <3rd centile)	Twins or other multiple pregnancy (uncomplicated)	Postpartum haemorrhage
	Abnormal placental shape	Polyhydramnios
Fetal hydrops	Two-vessel cord	Normal pregnancy
Maternal pyrexia (>38°C)	Prolonged rupture of membranes (>36 hours)	
	Gestational diabetes	
	Maternal group B streptococcus	
	Pre-eclampsia/maternal hypertension	
	Maternal coagulopathy	
	Maternal substance misuse	

Box 1. Process for storing and sending the placenta

- Store the placenta at 4°C in a tightly sealed container.
- The placenta must not be frozen as freezing obliterates the important microscopic features.
- Check whether criteria are met for histology.
- Use the placental referral proforma to record relevant clinical details.
- Label the specimen container with the patient's details.
- Submit the placenta to the laboratory in a fresh state.
- Formalin fixation is indicated if there is likely to be a delay in undertaking the examination, or when refrigerated storage is not available. Place the placenta in a sufficient sized container with an adequate volume of formalin to minimise distortion of the placenta.

West Midlands region.[4] A summary of the processes involved in storing the placenta and sending it for histological assessment is outlined in Box 1.

Normal placental development

Table 2 outlines the normal development of the placenta and its histological significance.[5]

Figure 1 shows the normal placental villous structure. Compare this with Figure 2, which shows abnormal placental histology with features of distal villous hypoplasia.

Placental assessment in cases of adverse pregnancy outcome

Maternal disease affecting the placental circulation or intrinsic placental pathology can lead to fetal growth restriction or stillbirth. Forty percent of stillbirths are associated with fetal growth restriction. In these cases, placental histology provides vital information as to the cause of adverse outcome and risk of recurrence. This is very important for managing subsequent pregnancies. The placenta may appear small, with a long and hypercoiled umbilical cord. Microscopy will confirm features such as advanced villous maturation, terminal villous hypoplasia, infarcts, decidual vasculopathy, massive perivillous fibrin deposition, fetal vessel thrombosis, chronic villitis of unknown aetiology and mesenchymal dysplasia.[6]

A retrospective review showed that knowledge of placental histology reduced the proportion of unexplained stillbirths. When considering consent for postmortem, women should be counselled that placental examination can provide critical information to understand what has happened and help plan future pregnancies.[7]

The first systematic review on histopathological examination of the placenta following stillbirth, which was published in 2014, confirmed that placental pathology led to stillbirth in more than 50% of cases. This review identified wide variation in the reporting of the clinical features of placental lesions and inconsistency in their classification. The review prompted the need for an international consensus for diagnostic criteria of abnormal placental features and stillbirth classification.[8]

In 2015, a group of pathologists produced a consensus statement agreeing on the criteria for placental sampling and the terminology used to describe placental lesions. This will enable international studies on placental pathology relevant to the clinical condition to be compared to generate best evidence.[9]

In 2015, Redline incorporated these criteria and classified placental lesions into three groups: vascular lesions, immune lesions and a third group of 'other' placental lesions comprising massive perivillous fibrin deposition, variation in placental shape and cord, placenta accreta and meconium-associated changes.[10]

Table 2. Significance of placental development and villous formation

Timescale	Stage of development	Histology	Significance
1–8 days post-conception	Blastocyst implantation	Differentiation of cytotrophoblast (CT) and syncytiotrophoblast (ST)	At this early stage, the growing embryo receives nutrition from endometrial cells by diffusion
8–13 days post-conception	Lacunar stage	Lacunae form in the ST mass	
12–15 days post-conception	Formation of chorionic plate	Chorionic plate composed of mesenchyme, CT and ST	
13–28 days post-conception	Early villous stage Primary villi formation Secondary villi formation Tertiary villi formation	Composed only of an outer layer of ST and a core of CT Mesenchymal core in the villi Fetal capillary within the mesenchymal core	Feto placental circulation is established Placental barrier separates the fetal and maternal blood streams
From fifth week	Differentiation of tertiary villi	Ramification of villous tree into different villous types by forming villous sprouts and trophoblastic sprouts	The different types of villi have different size, diameter and function
First and second trimester	**Villous differentiation:** Stem villi formation from mesenchymal and immature intermediate villi		
	Mesenchymal villi Precursor for other villi	Thick trophoblastic cover with prominent CT Primitive stromal core with loosely arranged collagen, fibroblasts Poorly developed fetal capillaries	Function: Early pregnancy: fetomaternal exchange and villous proliferation Late pregnancy: villous proliferation only At term, comprise less than 1% of the placental volume
	Immature intermediate villi	Bulbous in shape Thick trophoblastic cover, prominent CT Distinctive reticular stroma containing fluid-filled stromal channels Poorly developed capillaries	Function: Contributes to growth of villous tree only At term, comprises 5% of the placental volume
	Stem villi Found highest in the central subchorionic area of the placenta and the cord insertion site	Thick trophoblastic cover with identifiable CT Degenerative surfaces of the villi that are partially replaced by fibrinoid Stroma consists of condensed bundles of collagen fibre and blood vessels	Function: Mechanical support only At term, they make up to 20–25% of the placental volume
Third trimester	**Villous differentiation:** The mesenchymal villi differentiate into mature intermediate villi, which then produce terminal villi		
	Mature intermediate villi Precursors of the terminal villi	They are long and slender The stroma consists of loose connective tissue with numerous capillaries	Function: Significant role in fetomaternal exchange of respiratory gases and nutrients At term, they make up to 25% of the placental volume
	Terminal villi Outgrowths of the mature intermediate villi	Thin trophoblastic cover in intimate contact with capillaries defined by thin vasculo-syncytial membrane The capillaries possess a continuous endothelium and complete basal lamina. The connective tissue is scanty as the stroma is comprised of a majority of vascular lumina	Function: Significant role in fetomaternal exchange of respiratory gases and nutrients. At term, they comprise 45% of the placental volume

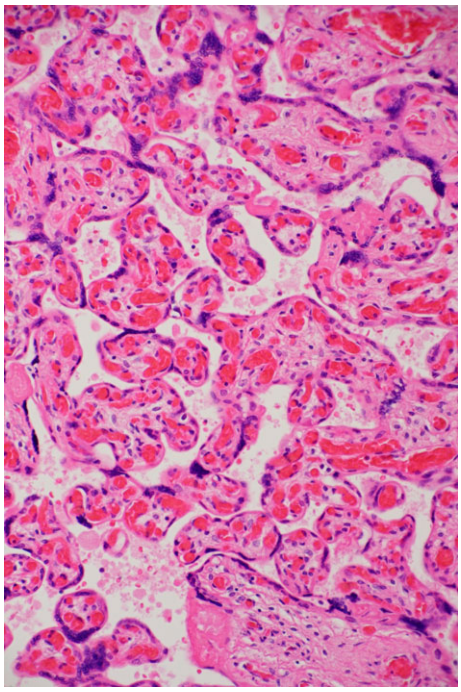

Figure 1. Normal term placenta. Villi are well vascularised with numerous vasculosyncytial membranes on the terminal villi.

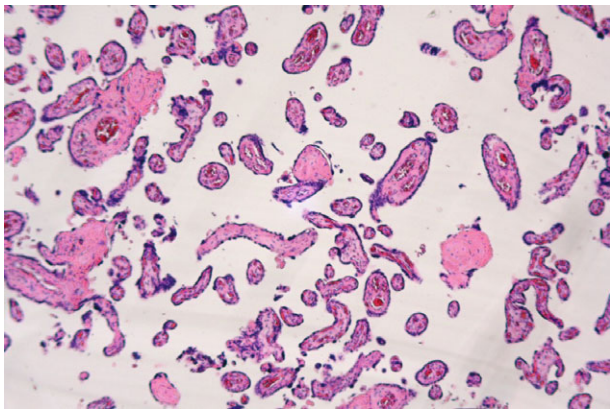

Figure 2. Severe distal villous hypoplasia. Note the small, sparse, fibrotic villi and the increased number of syncytial knots.

The implications of key placental histological findings are discussed below with reference to Amsterdam Placental Workshop Group criteria.

1. Maternal vascular malperfusion (MVM)
2. Massive perivillous fibrin deposition (MPVFD)
3. Fetal thrombotic vasculopathy (FTV)
4. Villitis of unknown aetiology (VUE)
5. Villous dysmaturity
6. Chorioamnionitis

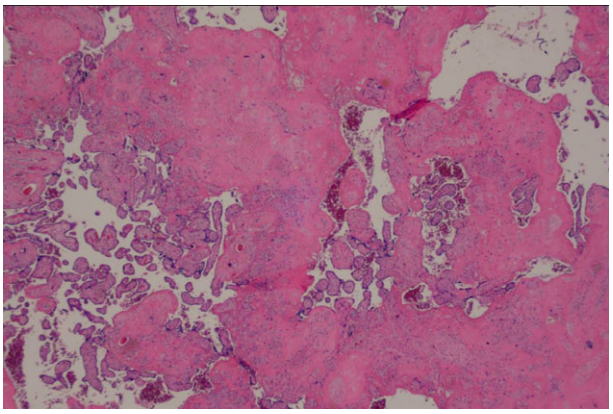

Figure 3. Massive perivillous fibrin deposition. Histology shows pale red fibrin encrusting the chorionic villi.

Figure 4. Massive perivillous fibrin deposition. Note the pearly, net-like deposition on the macro image.

Maternal vascular malperfusion (MVM)

According to the 2014 Amsterdam Placental Workshop Group criteria, MVM belongs to the group of placental vascular lesions.[9,10] MVM occurs as a result of abnormal spiral artery blood flow associated with maternal conditions such as pre-eclampsia. Redline describes the features as agglutinated villi, increased syncytial knots, distal villous hypoplasia (affecting more than 30% of distal villi) and infarcts.[10]

Distal villous hypoplasia, also known as terminal villus deficiency, is associated with post-placental hypoxia and fetal growth restriction, with absent or reversed end-diastolic flow. Microscopic features include the absence of terminal villus side branches of the mature intermediate villi and long, unbranched terminal capillary loops. Clinically, this results in a high Doppler resistance index (see Figure 2).[5]

Massive perivillous fibrin deposition (MPVFD)

MPVFD belongs to the third group of 'other' placental lesions.[10] It is a rare placental condition associated with

increased perinatal morbidity and mortality. MPVFD can occur at any gestational age. The condition is also known as maternal floor infarction (MFI), but histologically there are no signs of infarction, so some believe the term MFI to be a misnomer. MPVFD is associated with recurrent miscarriage, fetal growth restriction, stillbirth, preterm birth and neonatal neurological morbidity. It is characterised by the presence of excessive fibrin and a fibrinoid matrix surrounding at least 30% of distal villi (see Figure 3).[11]

The aetiopathogenesis of MPVFD is not clear. Macroscopically, the placenta appears yellowish in colour, stiff and thick. The maternal surface appears corrupted with loss of cotyledons. Microscopic changes include a net-like pattern of fibrinoids that completely cover the villi (see Figure 4). This then leads to degeneration of the syncytiotrophoblast and obliteration of fetal vessels.[5] The resultant clotting and fibrinoid plug closes the trophoblastic defects. The fibrinoid then heavily infiltrates the decidual floor. The villi appear to be choked and surrounded by dense fibrinoid material, leading to obliteration of intervillous space.[11]

The differential diagnosis of MPVFD includes normal perivillous fibrinoid deposition, chorionic villous ischaemia, fetal thrombotic vasculopathy and villitis of unknown aetiology. Individual histological features help to differentiate this condition from others.[11]

MPVFD is associated with significant adverse pregnancy outcomes. It is associated with fetal growth restriction in 24–100% of cases and with stillbirth in 13–50% of cases. There is a recognised association between MPVFD and certain clinical conditions, such as anti-phospholipid antibody syndrome and twin placentation. In a 2002 case series, Sebire et al. reported an association between women with MPVFD and anti-phospholipid syndrome.[12]

A retrospective study from a tertiary care centre in Ireland reported the incidence of MPVFD to be 0.28 per 1000 live births. The rate of stillbirth in this study was 31%, and 100% of live-born babies had restricted growth. The findings of this study suggest that fetal blood flow is compromised because of stromal fibrosis and a reduction in functional villi. Clinically, this leads to fetal growth restriction or stillbirth.[12]

Some studies have noted a high rate of recurrence of MPVFD (12–78%).[11] In the past, attempts have been made to diagnose this rare condition by antenatal scans to identify an indicative triad of growth restriction, thick hyperechoic placenta and oligohydramnios. Mandsager et al.[14] prospectively looked for these scan features in three women to predict placental changes. However, no other studies have further evaluated these ultrasound findings.[14]

The increased perinatal morbidity and the high recurrence risk associated with MPVFD makes it significant in clinical practice. Women who have had an adverse pregnancy outcome because of MPVFD should be counselled appropriately regarding a care plan in subsequent pregnancies.

Fetal thrombotic vasculopathy (FTV)

FTV belongs to the group of 'other' placental vascular processes involving fetal stromal vascular malperfusion.[10] It is associated with cord abnormalities such as hypercoiling, stricture, cord entanglement and long cord.

In 2014, a retrospective cohort study found a prevalence of FTV of 3.5% among placentas associated with adverse outcomes. The prevalence of FTV ranges from 1% to 6.4%.[15]

The aetiology of FTV is not known, but may be associated with:

1. a hypercoagulable state caused by fetal polycythemia or maternal thrombophilia
2. endothelial cell injury caused by a true knot, abnormal cord insertion, long or hyper-coiled cord
3. blood flow stasis or turbulence within the placental vessels caused by cord entanglement or stricture.[15]

FTV can occur as a result of placental or umbilical pathology. After blood vessel atrophy caused by occlusive thrombus, the villi will be avascular. Other characteristic pathological changes include an intimal fibrin cushion, fibromuscular sclerosis and haemorrhagic endovasculopathy.

Similar changes can be observed in the placenta after stillbirth. In FTV, the changes are focal and clearly demarcated from an adjacent normal villous structure. The placental changes after stillbirth are diffuse.[5]

Macroscopic placental changes are usually subtle. Late lesions with identifiable thrombus are grey–white in colour with a firm consistency. Microscopy shows thrombosed fetal vessels (see Figure 5). Avascular villi are confined to the single villous structure with normal vascularised villi in the adjacent area.[16]

In 2004, Redline et al. defined FTV as the "presence of 15 or more avascular villi or villous stromal–vascular karryorhexis in two or more foci per slide in the absence of villitis of unknown etiology."[17]

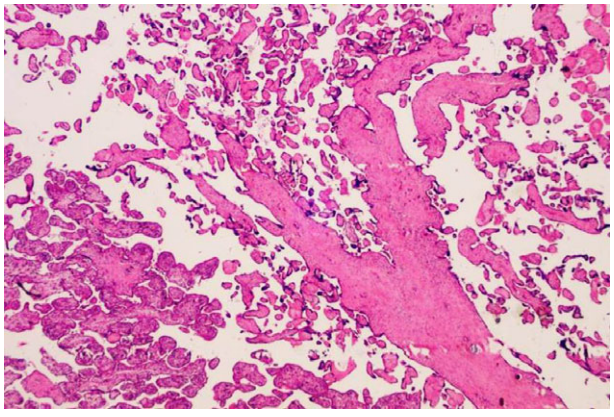

Figure 5. Fetal vessel thrombosis. Thrombosed vessel in large stem villus and downstream avascular villi are visible.

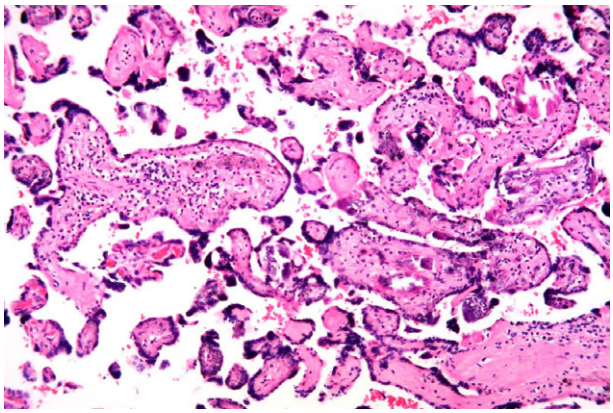

Figure 6. Villitis of unknown aetiology. Stem villi infiltrated by chronic inflammatory cells. Some of the villi in the vicinity are avascular. This is the consequence of chronic inflammation.

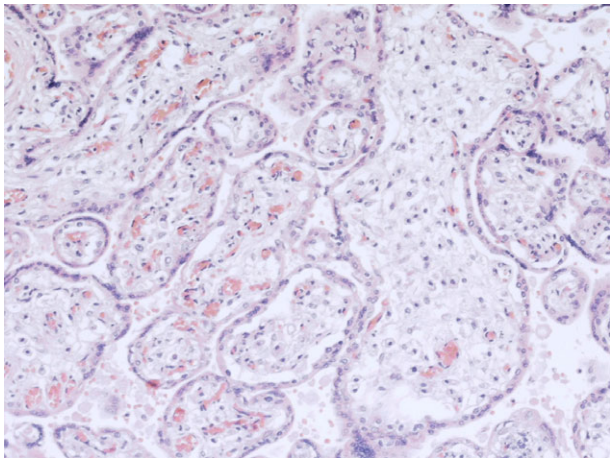

Figure 7. Villous dysmaturity. The villi are enlarged with increased distance between the surface of the villous and missing vasculosyncytial membranes.

Redline and Pappin studied placentas with features of FTV, confirming the association of avascular villi with clinical conditions including fetal growth restriction, oligohydramnios and fetal distress in labour.[18]

The following clinical conditions are associated with FTV:

- cord entanglement, hypercoiling or other cord abnormalities
- maternal or fetal thrombophilia
- severe chorioamnionitis
- pre-eclamptic growth restriction.

In 2004, a retrospective cohort study from the Netherlands confirmed the associations between pre-eclampsia, fetal growth restriction, neonatal thrombosis and FTV. This study reinforced the need for a standard approach to evaluate mothers who had experienced FTV and neonates presenting with thrombosis.[19]

Villitis of unknown aetiology (VUE)

VUE belongs to the group of placental inflammatory immune processes.[10] It is described as chronic inflammation with destructive changes and T cell infiltration into the chorionic villi.[20] The inflammation may be patchy or diffuse. VUE may be low or high grade in its nature (see Figure 6).

VUE is a common finding in 5–15% of near-term placentas. It is usually seen after 32 weeks of gestation; any prior gestational association is likely to be of infectious origin.[21] Inflammation is likely to be a graft versus host reaction. A higher incidence in women who have received a donor ovum further lends weight to this hypothesis. When found along with vasculopathy, associations with fetal growth restriction, recurrent pregnancy loss and neurodisability have been reported.

A retrospective study looked at the risk of recurrence of VUE in a subsequent pregnancy after an index pregnancy with an adverse event requiring placental histology.[22] A higher risk of recurrence was noted if the index pregnancy was reported to have high grade villitis. However, recurrent pathological findings did not necessarily translate to recurrent adverse outcomes. The significance of recurrence remains unknown.

A review of VUE reports associations with a variety of clinical outcomes including fetal growth restriction, twin discordance, idiopathic prematurity, hypertensive pregnancies and perinatal asphyxia. Associations with autoimmune and alloimmmune diseases have also been reported.[23]

The translation of this finding into clinical practice remains to be explored by future prospective placental histology studies. VUE may be suspected when higher levels of human chorionic gonadotrophin or alphafetoprotein, fetal growth restriction, or specific sonological indications of heterogenous placental pattern and focal sonolucent areas are detected in dedicated high-risk pregnancy units.

If found to be of clinical relevance and associated with adverse pregnancy outcomes in the future, it may be useful to explore the roles of aspirin or corticosteroids.

Villous dysmaturity

Villous dysmaturity belongs to the group of 'other' placental vascular processes involving fetal stromal vascular lesions associated with development.[10]

The association between villous dysmaturity and maternal diabetes is well recognised. On microscopic evaluation, the terminal villi appear enlarged, and there is an increased number of capillaries and macrophages, with fluid within the villous structure (see Figure 7). The increase in vasculosyncytial membrane appears to decrease the maternal and fetal exchange of oxygen and other nutrients.[5]

In 2008, Daskalakis et al. studied the placentas from 40 singleton pregnancies with maternal diabetes. Villous dysmaturity was recognised in 80% of the diabetic placentas compared to the control group. Other findings included villous

fibrinoid necrosis, chorangiosis and presence of nucleated fetal red blood cells. These histological features confirm the presence of chronic fetal hypoxemia associated with diabetic pregnancies.[24]

Chorioamnionitis

Chorioamnionitis belongs to the group of placental inflammatory immune processes.[10] It is defined as an inflammatory process affecting the chorion and amnion. Along with chorioamnionitis, fetal inflammatory response syndrome is comprised of villitis and funisitis (inflammation of the umbilical cord). The observed frequency of chorioamnionitis is higher in delivery at early gestation.[25]

In 2003, Redline et al. classified the inflammatory process according to its intensity:[26]

- grade 1 (mild to moderate): individual or small clusters of maternal neutrophils, diffusely infiltrating the chorion laeve, chorionic plate, subchorionic fibrin or amnion.
- grade 2 (severe): presence of three or more chorionic micro-abscesses, which are defined as a confluence of neutrophils measuring at least 10×20 cells. These are typically located between the chorion and decidua, and/or under the chorionic plate.

Microbial invasion of the amniotic cavity commonly occurs as ascending infection from the lower genital tract and rarely via the haematogenous route. Pre-labour rupture of membranes and a shortened cervix can increase the risk of amniotic infection. There is evidence to show that bacteria can invade the amniotic cavity, even with intact membranes.[26] Microbial invasion of the amniotic cavity then leads to an inflammatory response involving cytokines and neutrophils.

Table 3. Types of placental histology associated with adverse pregnancy outcomes

Adverse pregnancy outcome	Associated placental histology
Stillbirth	Placental abruption Fetal thrombotic vasculopathy Villous dysmaturity Maternal vascular malperfusion Massive perivillous fibrin deposition
Fetal growth restriction	Villitis of unknown aetiology Villous dysmaturity Fetal thrombotic vasculopathy Maternal vascular malperfusion Massive perivillous fibrin deposition
Spontaneous preterm delivery	Acute chorioamnionitis Marginal abruption
Neonatal neurologic comorbidities	Fetal thrombotic vasculopathy Umbilical cord accident Villitis of unknown aetiology Acute chorioamnionitis

Table 4. Clinical implications of placental histology

Placental histology	Clinical conditions	Implications in subsequent pregnancy
Severe global/partial MVM	Thrombophilia Pre-eclampsia Diabetes mellitus	Low dose aspirin Uterine artery Doppler Early third-trimester placental ultrasound Early delivery Recurrence risk: 10–25%
MPVFD	Thrombophilia Pre-eclampsia	Maternal autoimmune testing LMWH and low dose aspirin Intensive pregnancy surveillance Early delivery Recurrence risk: 40–60%
Villitis of unknown aetiology	Autoimmune disorders	Genetic counselling; maternal autoimmune testing; LMWH, low dose aspirin and/or immunosuppressive therapy Intensive pregnancy surveillance Early delivery Recurrence risk: 25–50%
Fetal thrombotic vasculopathy	Thrombophilia Severe chorioamnionitis	Maternal autoimmune testing Intensive pregnancy surveillance
Villous dysmaturity	Diabetes mellitus	Weight reduction Screen for gestational diabetes Advice to monitor fetal movements Consider delivery prior to 40 weeks of gestation

Key: MVM = maternal vascular malperfusion; MPVFD = massive perivillous fibrin deposition; LMWH = low molecular weight heparin

Clinical conditions associated with placental histology

See Tables 3 and 4 for a summary of clinical conditions associated with specific placental histological features and their implications in subsequent pregnancy.

Placental histology: cost and medicolegal implications

There are financial and resource implications involved in obtaining placental histology when required. In tertiary-level

National Health Service (NHS) hospitals, the service is provided by trained perinatal pathologists. However, there are some NHS hospitals where this service is not available; therefore, there is a significant cost to outsource to the resources at tertiary units. This cost implication must be balanced against the valuable information provided by placental histology. It is important that the referring hospitals follow clear protocols and ensure that placental histology is requested in appropriate clinical circumstances.

Placental histology is vital in medicolegal cases where there has been an unexplained adverse outcome. Placental histology findings, including villous dysmaturity and thrombotic vasculopathy, help to ascertain causes of stillbirth when there are no other clinical features to suspect a poor outcome. This also applies to cases in which babies are unexpectedly admitted to the neonatal unit for a variety of clinical reasons.

Conclusion

The key role of the placenta in fetal and neonatal mortality and morbidity cannot be overemphasised. This article presents the histological features of placental lesions that can contribute to adverse pregnancy outcomes. It is vital that obstetricians understand the importance of placental examination when they encounter an adverse pregnancy outcome. Regular meetings of a multidisciplinary team (including obstetricians, neonatologists and perinatal pathologists) should be held to discuss the correlation between placental histology and pregnancy outcome to help improve patient care in subsequent pregnancy.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

LT and KR researched and wrote the article. TM gave expert opinion and contributed to the histopathology slides. All authors approved the final version.

References

1 Gude NM, Roberts CT, Kalionis B, King RG. Growth and function of the normal human placenta. *Thrombosis Res* 2004;**114**:397–407.
2 Roescher AM, Timmer A, Erwich JJ, Bos AF. Placental pathology, perinatal death, neonatal outcome, and neurological development: a systematic review. *PloS One* 2014;**9**:e89419.
3 Hargitai B, Marton T, Cox PM. Best practice no 178. Examination of the human placenta. *J Clin Pathol* 2004;**57**:785–92.
4 Cox P, Evans C. *Tissue pathway for histopathological examination of the placenta*. London: Royal College of Pathologists; 2017[https://www.rcpath.org/resourceLibrary/tissue-pathway-histopathological-placenta.html].
5 Baergen RN. *Manual of pathology of the human placenta*. Heielberg: Springer; 2011.
6 Cox P, Marton T. Pathological assessment of intrauterine growth restriction. *Best Pract Res Clin Obstet Gynaecol* 2009;**23**:751–64.
7 Heazell AE, Martindale EA. Can post-mortem examination of the placenta help determine the cause of stillbirth? *J Obstet Gynaecol*. 2009;**29**:225–8.
8 Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of placental pathology reported in association with stillbirth. *Placenta* 2014;**35**:552–62.
9 Khong TY, Mooney EE, Ariel I, Balmus NC, Boyd TK, Brundler MA, et al. Sampling and definitions of placental lesions: Amsterdam Placental Workshop Group consensus statement. *Arch Pathol Lab Med* 2016;**140**:698–713.
10 Redline RW. Classification of placental lesions. *Am J Obstet Gynecol* 2015;**213**:S21–8.
11 Faye-Petersen OM, Ernst LM. Maternal floor infarction and massive perivillous fibrin deposition. *Surg Pathol Clin* 2013;**6**:101–14.
12 Sebire NJ, Backos M, Goldin RD, Regan L. Placental massive perivillous fibrin deposition associated with antiphospholipid antibody syndrome. *BJOG* 2002;**109**:570–3.
13 Bane AL, Gillan JE. Massive perivillous fibrinoid causing recurrent placental failure. *BJOG* 2003;**110**:292–5.
14 Mandsager NT, Bendon R, Mostello D, Rosenn B, Miodovnik M, Siddiqi TA. Maternal floor infarction of the placenta: prenatal diagnosis and clinical significance. *Obstet Gynecol* 1994;**83**:750–4.
15 Lepais L, Gaillot-Durand L, Boutitie F, Lebreton F, Buffin R, Huissoud C, et al. Fetal thrombotic vasculopathy is associated with thromboembolic events and adverse perinatal outcome but not with neurologic complications: a retrospective cohort study of 54 cases with a 3-year follow-up of children. *Placenta* 2014;**35**:611–7.
16 Marsden L, Comstock J. Fetal thrombotic vasculopathy. *J Fetal Med* 2015;**2**:121–5.
17 Redline RW, Ariel I, Baergen RN, Derek J, Kraus FT, Roberts DJ, et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol* 2004;**7**:443–52.
18 Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. *Hum Pathol* 1995;**26**:80–5.
19 Leistra-Leistra MJ, Timmer A, Van Spronsen FJ, Geven WB, Van der Meer J, Erwich JJ. Fetal thrombotic vasculopathy in the placenta: a thrombophilic connection between pregnancy complications and neonatal thrombosis? *Placenta* 2004;**25**:S102–5.
20 Kim CJ, Romero R, Chaemsaithong P, Kim JS. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. *Am J Obstet Gynecol* 2015;**213**:S53–69.
21 Redline RW. Villitis of unknown etiology: noninfectious chronic villitis in the placenta. *Hum Pathol* 2007;**38**:1439–46.
22 Feeley L, Mooney EE. Villitis of unknown aetiology: correlation of recurrence with clinical outcome. *J Obstet Gynaecol* 2010;**30**:476–9.
23 Boog G. Chronic villitis of unknown etiology. *Eur J Obstet Gynecol Reprod Biol* 2008;**136**:9–15.
24 Daskalakis G, Marinopoulos S, Krielesi V, Papapanagiotou A, Papantoniou N, Mesogitis S, et al. Placental pathology in women with gestational diabetes. *Acta Obstet Gynecol Scand* 2008;**87**:403–7.
25 Kim CJ, Romero R, Chaemsaithong P, Chaiyasit N, Yoon BH, Kim YM. Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance. *Am J Obstet Gynecol* 2015;**213**:S29–52.
26 Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C, et al. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol* 2003;**6**:435–48.