On perinatal pathology
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Abstract

The placenta is often not submitted for histopathological examination and obstetricians may be sceptical of the value of the examination. This article looks at the reasons for histopathological assessment of the placenta, examines what clinical information should be provided to pathologists and reviews what information can be gained from this ‘diary of the pregnancy’, especially for explaining adverse outcomes and potentially guiding the management of future pregnancies.
Introduction
Until recently, most maternity units would practise a rather strange ritual with the placenta. After birth it would be examined closely by the midwife, weighed (this was recorded for posterity in the birth register) and then be put in the fridge for a few days, in case someone wanted to look at it prior to being discarded. Rarely was it thought to be of value to send this remarkable organ to an expert for histopathological examination. It is now more commonplace for placentas to be presented for further studies, although many obstetricians may still be sceptical about the value of this investigation. This article looks at the reasons for histopathological assessment of the placenta, examines what clinical information should be provided to pathologists, and discusses lesions that should be recognised and commented upon by the pathologist in the report. It reviews what information can be gained from this 'diary of the pregnancy', especially for explaining adverse outcomes and potentially guiding the management of future pregnancies.

Which placentas require histopathological assessment?
The placenta remains a neglected source of discovery, although in 30-64% of placentas an indication for the cause of adverse pregnancy outcome can be found in the placenta.1-3 The College of American Pathologists (CAP) published guidelines in 1997 for pathological assessment of the placenta.4 Despite this, Badawi et al. found only 11.2% of placentas were examined, although according to the guidelines developed by CAP 43.3% had an indication for examination.5 Spencer et al. found that only 32% of placentas with an indication (following the CAP guidelines) were examined.6 Similar figures have been reported from the USA.7 While there are no Australian guidelines for placental examination, many obstetric departments adopt modified forms of these CAP guidelines.

From recent medicolegal cases in Australia it is surprising how often placental examination is not requested in cases when a baby has been born unexpectedly 'flat' and with a putative diagnosis of perinatal asphyxia. Although placental abnormalities do not necessarily mean that there has not been any negligence in treatment around the time of birth, it can help to provide a more complete picture of what may have happened earlier in the pregnancy before the obstetrician had a reasonable chance to intervene. Placental pathology may point to a pre-labour cause of fetal hypoxia and neurological damage8 and is particularly valuable in cases of stillbirth due to congenital infection when parents do not agree to perinatal autopsy.
Standardised clinical information
For the pathologist to interpret the placental pathology it is important to be adequately informed about the circumstances of the patient’s pregnancy and relevant medical history. It is known that, in general, medical history details are usually not well provided on pathology request forms. Because the placenta is dynamically growing during the short period of gestation and the responses to various insults may appear similar, this information is vital for the pathologist to interpret in line with the pathology findings. No studies are available regarding the results of histological assessments by pathologists either provided with or blinded for clinical history or information of current pregnancy; however, clinical information is necessary for complete assessment and the potential to draw conclusions regarding the pathophysiological pathways. These pathways could lead to adverse maternal or fetal outcomes, including death, and may also help in determining recurrence risks.

How much information should be provided on the request form? Uniformly presented relevant medical and obstetric history provides clarity and use of a standard format for this is helpful. The presented data should include maternal age, gravidity, parity, fetal losses, vascular disease, uterine abnormalities, systemic diseases such as hypertension, infections, caesarean(s), and also relevant family history regarding congenital anomalies and systemic diseases. Secondly, information on the current pregnancy should include: gestational age, medication, smoking and drug or alcohol use, bleeding or infection, abnormalities discovered at ultrasonographic examination, diseases in pregnancy such as infections, trauma or antepartum haemorrhages, pregnancy related diseases such as preeclampsia or gestational diabetes. Finally, information of circumstances around birth should be recorded: estimated weight (expected or unexpected intra-uterine growth restriction/macrosumia), interval of rupture of membranes, meconium-stained amniotic fluid or not, duration of labour, signs of infection, cardio-tocographic abnormalities, mode of delivery, APGAR scores, congenital abnormalities of the baby (gross examination), fetal sex and birth weight, and abnormalities of placenta. Developing a standard form for placenta examination request, with the items mentioned above, can facilitate this type of communication between obstetrician and pathologist. Standardised request forms have been shown to improve submission rates for placental examination.
What common placental lesions have recurrence risks?

There have been several recent reviews and monographs on the examination of the placenta.\textsuperscript{10-16} It does appear that some placental lesions have a recurrence risk, although it is unclear to what extent obstetricians are aware of these risks. Some of the more common lesions are discussed below.

Chronic villitis is defined as a lympho-histiocytic inflammation of the terminal villi (Figure 1). Chronic villitis may be associated with some viral infections but most are nonspecific and not associated with known pathogens; hence the term ‘villitis of unknown aetiology’. A bacterial aetiology has not been found for chronic villitis.\textsuperscript{17} The exact pathogenesis remains unclear: it could be due to pathogens that are as yet unrecognised or due to a maternal-fetal immunological reaction. Support for the latter comes from the finding that approximately 50% of the inflammatory infiltrate in the villous stroma is maternal in origin\textsuperscript{18,19} and also that non-specific chronic villitis is associated with maternal autoimmune disease and with oocyte donor pregnancies.\textsuperscript{20} Non-specific villitis may be associated with intrauterine growth restriction, preterm labour and fetal death and may be recurrent in up to 17% of cases.\textsuperscript{11}

Thrombophilia effects on the placenta are being increasingly recognised and reported. Although the association of adverse obstetric and fetal outcomes with various thrombophilias have been questioned, there is potential of recurrence because of the heritability of the haematological condition.\textsuperscript{21} Thrombosed fetal vessels can sometimes be discerned on the chorionic plate. Thrombotic or occlusive lesions in the placenta can be seen as white plaques grossly on the placental slices or as avascular villi on microscopy (Figure 2). The term ‘fetal thrombotic vasculopathy’ has been used to describe this and other lesions, such as fibromuscular sclerosis of stem villous vessels, haemorrhagic endovasculitis, and fetal artery thrombosis.\textsuperscript{22} The tracts of avascular villi are seen more often than frank thrombosis and there is usually a clear demarcation between the vascular and avascular portions of the placenta. Upstream from these avascular villi is the likely location of a thrombosed stem artery (Figure 3). It is evident that dislodged fragments of the thrombus can easily embolise to the fetal brain through the paradoxical fetal circulation and cause perinatal stroke, leading to subsequent neurological impairment.\textsuperscript{23}

The finding of acute chorioamnionitis or evidence of amniotic fluid infection may affect management of future pregnancies. Bacterial vaginosis has serious implications during pregnancy, as it has been associated with adverse outcomes such as chorioamnionitis, late miscarriage, premature rupture of membranes and preterm birth.
The organisms implicated include Gardnerella vaginalis and Mycoplasma hominis. The infection recurrence rate is high, even in treated women, due to relapse and reinfection.\textsuperscript{24} and the value in placental examination would be more for documenting the role of the infection in the index pregnancy than in screening in the next pregnancy. Group B streptococcus infection is associated with preterm labour and can be recurrent.\textsuperscript{25} Most obstetricians would modify their management of the next pregnancy if the index pregnancy was affected by Group B streptococcus.

![Figure 1](image1.png) ![Figure 2](image2.png) ![Figure 3](image3.png)

**Figure 1.** Chronic villitis showing infiltration of villous stroma by lymphocytes and histiocytes (H&E, high power). Figure 2. Fetal thrombotic vasculopathy. Tracts of avascular villi are clearly demarcated from the vascular villi (H&E, low power). Figure 3. Thrombosed fetal vessel in the chorionic plate in a case with fetal thrombotic vasculopathy (H&E, medium power).

Inherited metabolic disorders may sometimes be diagnosed at placental examination, especially in cases of fetal hydrops and stillbirths. Some may have recurrence risks.

Documentation of various pathologies is not merely an exercise for pathologists. It has relevance for obstetricians, although interventions and treatments for those pathological processes that may be recurrent are still quite limited. Perhaps the most important is increased fetal surveillance with chorionic villous sampling, ultrasound biometry and Doppler assessment of umbilical and uterine artery blood flows in future pregnancies. Early delivery is often advocated for such things as severe placental abruption or unexplained stillbirth. If the placental pathology has pointed to a thrombophilia or similar process then lowdose aspirin or low molecular weight heparin might be used. Whether or not there is a place for immunosuppressive treatments such as corticosteroids for conditions such as villitis of unknown origin is unclear and must
Histopathological examination of the placenta: key issues for pathologists and obstetricians

await the outcome of future clinical trials. The detection of infection, such as group B streptococcus, can be managed with peripartum antibiotics.

The placental report as information for the obstetrician

New placental abnormalities are still being defined or their definitions refined. Recently, attention has been drawn to the coiling index of the umbilical cord as this has been related to an adverse pregnancy outcome.\textsuperscript{26,27} An umbilical cord without any coiling was described as raising the risk of intrauterine fetal death for the first time in 1993.\textsuperscript{28} A year later abnormalities in umbilical coiling were related to meconium stained amniotic fluid, intrauterine death, preterm delivery, intrapartum heart rate abnormalities, operative delivery for fetal distress and karyotypical abnormalities.\textsuperscript{29} It has been advised that any placenta with abnormal coiling should be sent to the pathologist for evaluation. The clinical consequences, such as antenatal ultrasound measurements of the coiling index, are not yet clear as the exact mechanism that eventually determines the coiling index at different gestational ages is still under debate (is it the first step in the causal pathway or a consequence of something else?).\textsuperscript{30} The abnormal coiling index remains an unknown or unrecognised abnormality for many clinicians and it may be an important lesion for the pathologist to document when examining the placenta. Pathologists and clinicians should educate one another on topics such as coiling indexes, for better research and follow-up, with potential consequences for future pregnancies. For example, the antenatal ultrasound finding of a diminution of coiling from the fetal to umbilical end of the cord may be confirmed post-delivery but the correlation with gestational age cannot.\textsuperscript{31,32} Pathologists often receive only part of the cord for examination and this may hamper comparative studies.

In clinical practice, preterm birth may result from either ischaemic or infectious lesions which can be confirmed by placental examination.\textsuperscript{33} The clinical diagnosis of infection can be difficult for several reasons: maternal fever and fetal tachycardia could be due to epidural analgesia, which can also mask abdominal pain.\textsuperscript{34} In clinically suspected chorioamnionitis, evidence is brought by histopathological evaluation in approximately 60\% of cases. Histological evidence better correlates with fetal signs than maternal signs for infection.\textsuperscript{35} If chorioamnionitis is seen, approximately 70\% of cultures or PCR will be positive.\textsuperscript{36,37} However, chorioamnionitis does not necessarily equate to fetal infection.\textsuperscript{38} Besides these difficulties in diagnosis of chorioamnionitis and infection, the placentas of suspected infections are often not even presented for pathology examination.
Several placentation disorders and placental abnormalities that can be discovered by ultrasound examination have been described. These abnormalities may not have much significance in daily practice, as in case of echolucencies or calcifications in the term pregnancy, but these abnormalities are easily detected at pathology examination. The same abnormalities in a preterm placenta, however, may be a cause for concern as placental function can be impaired. How well the ultrasound recognition of placental pathology correlates with what is found on placental histopathology is unclear and requires much more systematic research. Unlike studies that have examined correlation between ultrasound and pathological findings in fetuses, no clear data are available on ultrasound detection rates and their correlation with pathology results. It is not always possible to confirm ultrasound diagnosis by placental examination, for example in the case of vasa praevia, as the exact location of the velamentous vessels remain unknown. Other ultrasound diagnoses, such as twin-to-twin transfusion syndrome and chorangioma, can be confirmed by pathology. Although demonstration of vascular anastomoses does not necessarily equate with a twin-twin transfusion syndrome, nevertheless such examination should be performed in all monochorionic twin placentas. Parenthetically, the identification of two yolk sac remnants on placental examination or the finding of a fetus papyraceous would indicate a twin pregnancy, the former being a vanishing twin; this has effects on the surviving twin. Some placental abnormalities with clinical consequences are obvious at placental examination but hard to observe at ultrasonography, such as (recent) infarctions and placental abruptions. Other abnormalities can be detected by ultrasound but many false positive cases can be expected, such as with placenta circumvallata.

What does the obstetrician require from the pathology report?
Placental reports should provide the necessary information for the clinician to be able to counsel the parents and provide an explanation of possible pathophysiological pathways leading to the adverse outcome, their recurrence risks and possible interventions in future pregnancies. In an assessment of the quality of placental reports, the pathologist commented on gross histopathological abnormalities in 42-86%, on relation with clinical situation in 43-94%, and on recurrence risks in 0-50% (and in case of twin pregnancy on zygosity in 0-44%). Communication is very important between pathology and other specialties; both parties should make sure that the other is well informed with understandable language and explanations on their part. In surgery it has been described to be useful to organise multidisciplinary meetings including
a pathologist for early refining of diagnosis. The involvement of the pathologist in similar meetings with obstetricians and neonatologists may be equally as informative, particularly in the case of apparent unexplained stillbirth or serious adverse outcome.

This is perhaps one area of clinical obstetric practice where the clinician would really welcome the pathologist to be as directive as possible and to provide as much information as possible about the significance of the placental lesions identified, the likely causality with any adverse outcome, and the possibility of recurrence in future pregnancies. For most obstetricians, adverse outcomes are encountered relatively infrequently in their obstetric practice and the pathologist should not assume that there is any more than a basic knowledge of the significance of placental pathology. A description of what is seen down the microscope, using unfamiliar histopathological terms, without any discussion of the significance is of little value to all but the most informed and educated subspecialist with a special interest in placental pathology. Most obstetricians would agree with the statement 'Tell us what you see, and tell us what it might mean!' As with all medicine, optimal patient care requires good communication.
Reference list