Placenta xxx (2016) 1–5

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

# Implications of placental pathology for disease mechanisms; methods, issues and future approaches

Neil James Sebire

*Department of Paediatric Pathology, Great Ormond Street Hospital, London, WC1N 3JH, UK*

ARTICLE INFO

*Article history:*
Received 4 March 2016
Accepted 10 May 2016

*Keywords:*
Placenta
Pathology
Proteomics
Transcriptomics
Blinding

ABSTRACT

Pathological examination of the placenta is a well-established investigation following delivery in order to investigate the underlying mechanisms of a range of pregnancy related complications. Several recommendations and guidelines are available regarding the indications for such placental testing. The immediate clinical rationale for this process is to identify underlying disease processes which may have an impact on the management of either the infant or the mother in future pregnancies. Additional benefits include improved understanding of the pathophysiological processes of disease and potential medico-legal implications in cases with adverse outcome, including regarding possible timing of lesions. However, interpretation of findings in specific cases remains difficult for several methodological reasons. Future progress requires the use of high quality, well phenotyped tissue collections, with blinded assessment using consensus criteria. In addition, it is likely that novel discovery-based approaches will significantly change the concept of how placental disease is investigated, making tissue sampling even more important across a wide range of pregnancy-related diseases. This will be associated with more stringent conditions for placental evaluation and sampling, including strict definitions of sample site and interval post-delivery, the effects of which will vary depending on the precise assays and methodologies used.



## 1. Introduction

Pathological examination of the placenta is a well-established investigation following delivery in order to investigate the underlying mechanisms of a range of pregnancy related complications. Several recommendations and guidelines are available regarding the indications for such placental testing [1,2]. The immediate clinical rationale for this process is to identify underlying disease processes which may have an impact on the management of either the infant or the mother in future pregnancies. However, additional benefits include improved understanding of the pathophysiological processes of disease and potential medicolegal implications in cases with adverse outcome, including regarding possible timing of lesions [3]. Due to the specialist nature of diseases affecting the placenta, such specimens should be examined by dedicated paediatric and perinatal pathologists rather than general pathologists; in one study, 40% of placental reports generated by non-specialist pathologists contained errors, predominantly errors of exclusion but also including false positive diagnoses [4].

The standard approach to placental examination for clinical purposes includes weighing and measuring of the placenta, (and associated cord and membranes), followed by detailed inspection, and systematic sectioning of the placental parenchyma to identify macroscopic lesions. Tissue blocks are then routinely obtained from the cord, membranes and representative areas of the placenta proper for subsequent formalin fixation, processing, paraffin embedding and cutting for histological examination and reporting. It should therefore be noted that while a wide range of specialist techniques are available, these are not routinely performed. Furthermore, the sampling protocol described above is predominantly for clinical purposes. The tissue requirements for many research studies will therefore likely not be served by routine placental handling protocols used in the clinic. For example, rapidly obtained, snap frozen tissue is not routinely obtained in most clinical services. Specific and targeted placental research projects often require dedicated additional protocols in order to obtain tissue of the appropriate type and quality. Details of the precise sampling protocols for different types of research study are discussed in detail in a recent position paper/guideline in this journal [5].

*E-mail address:* neil.sebire@gosh.nhs.uk.

http://dx.doi.org/10.1016/j.placenta.2016.05.006
0143-4004/

## 2. Contributions of placental pathology to disease pathophysiology

The histological evaluation of placentas from different patient groups has illuminated our understanding of the underlying disease processes which may result in a range of clinical phenotypes. Two examples to illustrate this area are preterm birth (PTB) and intrauterine growth restriction (IUGR). Studies of PTB have determined that a major cause is ascending genital tract infection, which has a strong relationship to gestational age; chorioamnionitis affects the great majority (>80%) of mid trimester spontaneous losses and severe early preterm deliveries, whereas this is less common towards term, where it affects around 10% of deliveries [6]. Other causes of PTB include changes of maternovascular malperfusion (MVM; see below), but other cases may demonstrate no significant placental pathology, and are likely a consequence of maternal factors such as cervical incompetence or idiopathic onset of preterm labour [7,8]. The finding that several categories of disease and mechanisms may result in an apparently common clinical phenotype is important, since it allows targeted strategies to be derived specific to each mechanistic group.

Similarly, studies examining placental findings in IUGR across all gestations have reported that around one half of cases demonstrate features of typical maternovascular malperfusion (MVM) secondary to impaired trophoblast invasion with defective conversion of uterine artery branches into low resistance uteroplacental vessels [9,10]; Fig. 1. It is further recognised that there is significant overlap between features of early onset IUGR and early onset pre-eclampsia (PET), sharing common placental changes. More recently, there has been wider appreciation that early versus late-onset IUGR and PET show differing patterns of pathology, with late onset cases often associated with minimal placental histological abnormalities suggesting that these entities may have different underlying mechanisms, with more late onset cases associated with impaired maternal adaptation [11]. Finally, as with PTB, smaller subgroups may demonstrate other, specific, pathologies, such as chronic histiocytic intervillositis or massive perivillous fibrin deposition, whilst others may be associated with no significant morphological abnormalities, their mechanisms remaining uncertain, but for example, being due to impaired transport functions.

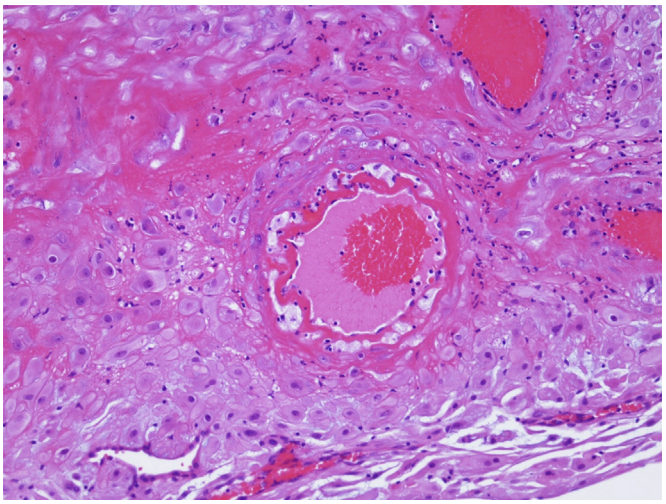

**Fig. 1.** Photomicrograph of a maternal decidual vessel demonstrating pathological changes of atherosis, with fibrinoid change and foamy macrophage infiltration of the subintimal region. (Haematoxylin and Eosin, original magnification ×100) These changes indicate significant maternal vasculopathy, which may be associated with a range of underlying conditions and complications such as pre-eclampsia.

## 3. Issues with placental pathology approaches

Despite the undoubted value of placental histological evaluation for recognition of patterns of underlying pathophysiology in groups of patients, there are several difficulties with the traditional approach on which much of the existing data is based. Firstly, placental histological evaluation is in many ways more difficult than other areas of diagnostic pathology, such as oncology for instance, since in the majority of cases, there are few morphological findings that are unequivocally diagnostic of a particular condition or phenotype, and no specific immunostain or routine molecular investigation can provide a definite 'gold standard' diagnosis. For most conditions, such as IUGR, there are few pathognomonic lesions which are never encountered in clinically uncomplicated pregnancies, (with the probable exception of acute atherosis), and most of the findings in IUGR simply occur more frequently, and in different combinations, than in controls [12]. This requires a subjective assessment of the significance of such features in a given case meaning that when evaluating data from retrospective studies it is often impossible to separate the objective findings present from the subjective interpretation of such findings, which may obviously vary according to the reporting pathologist.

Furthermore, in general, for individual cases there is poor correlation between the extent of histological changes and clinical severity of disease. This is likely in part due to sampling issues, but also because of the varied underlying mechanisms and maternofetal interactions which may result in a clinical phenotype. For example, in term PET, even clinically severe disease may be associated with only mild morphological changes of the placenta [13].

### 3.1. Poor clinical phenotypes

A further significant difficulty in interpretation of placental findings is related to the loose clinical phenotypes used for both cases and controls in many historical studies. For example, the majority of the literature regarding IUGR is based on the 'case' group being identified as birthweight <10th centile, this representing SGA rather than pathological IUGR. Around half of all cases of SGA are likely normal small rather than pathologically growth restricted and hence inclusion of all as 'SGA cases' will by definition include a mixture of normal and pathological pregnancies [14]. In addition, 'controls' are often identified as cases submitted for histological assessment due to a clinical indication which differs from the 'case' group, rather than truly being matched normal controls. This situation is obviously exacerbated in cases with preterm delivery since normal controls largely do not exist.

It is now increasingly recognised that rather than extremely large studies with loose inclusion criteria, higher quality data to answer specific questions can be derived from studies including smaller numbers of patients but with extremely strict entry criteria to ensure that the category of interest is as well represented as possible without 'dilution' by other disease phenotypes [15].

### 3.2. Interpretation of lesions; blinding and bias

Since clinically submitted cases requiring a formal histopathology report require interpretation of findings in light of the clinical information, the majority of such cases are not reported blinded to the patient history or other findings. These factors can significantly influence the content of the report and hence retrospective series of clinical reports provide relatively poor quality data for targeted scientific studies. It has been demonstrated, for example, that dating of placentas is poor even by experts, and that the gestational age stated on the request form has a major influence on the apparent interpretation of gestational age performed by

Please cite this article in press as: N.J. Sebire, Implications of placental pathology for disease mechanisms; methods, issues and future approaches, Placenta (2016), http://dx.doi.org/10.1016/j.placenta.2016.05.006