Placental Pathology
for general pathologists

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Placental examination

Placental pathologies
Common issues/mistakes
Problems with existing data
Future approaches
Routine tissue handling in Placental Pathology

Delay from delivery to fixation / sampling (4 degrees)
1-48 hrs

Formalin fixation
Inhibits autolysis (rapid)
Structurally cross links proteins (slow)

Staining
Embedding to paraffin
Block taking
Techniques in Placental Pathology

Morphometry

Histomorphology

Histomorphometry / stereology

Injection studies

Expression / OMICS

Immunostaining
Placental examination

Why bother?

Recurrence risk
Neonatal management
Maternal management
Pathophysiology
Medicolegal aspects
Value of placental examination: Operator dependancy

- 40% erroneous reports
- 90% omissions
- 10% overdiagnosis

> other subspecialities

Sun et al 2002
Difficulties with placental pathology

- Poor clinical phenotypes
- Definition of lesions / use of terminology
- Interpretation of lesions
- Blinding and bias
Consensus on features of:

- Maternovascular malperfusion
- Fetalplacental malperfusion
- Stem vessel occlusion
- Intramural fibrin deposition

No consensus on other ‘hypoxic’ features
No consensus on clinical significance / correlates
Most common issues / mistakes......

- Not knowing the implications of the clinical details
Most common issues / mistakes......

- Not knowing the implications of the clinical details ....

- ‘Overfitting’ findings to the clinical details!
Most common issues / mistakes......

- Not knowing the implications of the clinical details ....

- ‘Overfitting’ findings to the clinical details!

- Underestimating importance of macroscopic findings (depending on hx.......)

Most common issues / mistakes......

- Not knowing the implications of the clinical details ....

- ‘Overfitting’ findings to the clinical details!

- Underestimating importance of macroscopic findings (depending on hx.......)

- Not recognising rare entities
Most common issues / mistakes......

- Not knowing the implications of the clinical details....

- ‘Overfitting’ findings to the clinical details!

- Underestimating importance of macroscopic findings (depending on hx.......)

- Not recognising rare entities

- Overcalling normal variants
Macroscopic abnormalities

Shape
Cord insertion
Abnormal vessels
Abruption
Infarcts
Jelly-like
Other (?MPVFD)
Retroplacental haematoma / abruption

Feature of uteroplacental disease

Association with:
Pre-eclampsia
Smoking
Cocaine
Thrombophilias
PROM / Chorioamnionitis
Placental abruption

- Clinical abruption - 30% histo confirmation
- Retroplacental haematoma histo – 35% Hx abruption
  Clinical abruption 1% pregnancies

Histology: congestion+retroplacental haem+compression+acute infarct
Placental Examination: Cambridge Study

- 1,159 singleton unselected women recruited at booking
- Objective measurements from calibrated images
- Histological exam, routine blocks
- Two paediatric pathologists
- Blinded to all clinical information - study number only

Pathak et al 2011

Total population
- Age 29
- GA 39 weeks
- PET 2%
- PIH 3%
- SGA 6%
Placental Examination: Cambridge Study

Fig. 3. (a) Frequency histograms of cord centrality index at 37–42 weeks; 
(b) explanatory photograph of a placenta showing cord centrality index of 0.36.

Fig. 4. (a) Frequency histograms of placental eccentricity at 37–42 weeks; 
(b) explanatory photograph of a placenta showing eccentricity of 0.49.
Aetiology of spontaneous PTB:

Studies of pathology

30-50% infection / inflamm

20-30% uteroplacental disease / ischaemic?

20-30% No pathological entity

Salafia et al 1992, Arias et al 1993
Aetiology of spontaneous PTB
Chorioamnionitis / choriodecidual inflammation

Sebire et al 2001

Majority of severe preterm births
Sampling from rupture site
Interpretation
Relevance to management
Ascending genital tract infection

Sequence - local, CODIS, CA, fetal response, funisitis

Relation to short cervix, progesterone Rx, mucous effects, etc ?????
Chorioamnionitis and brain injury

Histologic CA in term infants relation to CP

RR 8.9 (95% CI 1.9-40)

? direct effect or via chorionic plate thrombi

Wu et al 2003
Placental changes described in FGR
Pathology of FGR / PET

Impaired trophoblastic invasion

Reduced or abnormal uteroplacental blood flow

Impaired oxygen delivery

Abnormal uteroplacental pressures

Secondary effects on fetoplacental flow
Placental changes in FGR

- Smaller size
- Reduced surface area
- Villous hypovascularity
- Decidual vasculopathy
- Infarcts
Placental changes in FGR

- Reduced villous branching
- Increased Maturation / Terminal villous hypoplasia
- Villitis
- Transporter and growth factor alterations
- Increased apoptosis
- Shorter telomeres
- NRBCs
Other microscopic / molecular abnormalities in FGR

Villitis
CHI
Functional abnormalities
Villitis of unknown aetiology

Mechanism?

CD68 macrophages, CD3 T-cells

Mainly maternal

?Immune dysregulation

Redline & Patterson 1993; Kapur et al 2004; Myerson et al 2006
Villitis of unknown aetiology

Clinical significance?

7.6%-13.6%-25%

Association with IUGR, PET OR SGA - 2.5

Russell 1980; Labarrere et al 1982; Knox & Fox 1984; Labarrere et al 1986; Becroft et al 2005
Chronic histiocytic intervillositis
Chronic histiocytic intervillusitis

Miscarriage / IUD - 80%
20% pregnancies reach term
30% viable IUGR
High recurrence risk (70%)

Immunological mechanism
Optimal treatment unknown

CD68

CD3
MFI / MPVFD

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Fetal loss</th>
<th>IUGR</th>
<th>Preterm</th>
<th>Recurrence</th>
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<td>Bane &amp; Gillan 2003</td>
<td>1/3500</td>
<td>31%</td>
<td>100%</td>
<td>33%</td>
<td>18%</td>
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<tr>
<td>Katzman &amp; Genest 2002</td>
<td>1/244</td>
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<td>40%</td>
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Summary of Placental Pathology findings in FGR

MVM

Normal

VUE

CHI, MPVFD

FTV

Placental changes in IUGR; problems...

Poor correlation with Doppler or severity (infarcts and atherosis best)

No lesion pathognomonic, many are histologically normal (approx 30-50% vs 70% controls)

Infarct 25-40 vs 10-15% controls
Villitis 8-21 vs 3-5% controls
Maturation/knots 90% vs ???
Plasma PI GF at presentation with SGA
Low PI GF best predictor of ‘placental FGR’ (mixed methods and criteria but infarcts, abruption, MVM)
N=196 FGR with abn UAD, stratified by screening UtAD
Abn UtAD ass with MVM (80%)
UtAD ass with less MVM (25%) but more CHI (16%), FTV (26%), DVI (11%) and MPVFD (21%)
Methodological issues

- Poor clinical phenotypes
- Definition of lesions
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Pathak et al 2011-
OR vs PPV for placental ‘lesions

Atherosis

VUE

Chorioangioma

FTV
OR vs PPV for placental 'lesions

<table>
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<tr>
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<th>VUE-yes</th>
<th>VUE-no</th>
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<tr>
<td>PIH</td>
<td>3</td>
<td>24</td>
<td>3.21(1.0-10.54)</td>
<td>7.9%</td>
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<tr>
<td>Normal population</td>
<td>35</td>
<td>900</td>
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<td>0.11(0.04-0.27)</td>
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Changes in transfer FUNCTION not detected

Pathophysiology of abnormal fetal growth complex and poorly understood
Much related to placental dysFUNCTION
Cord blood metabolomic profiling in intrauterine growth restriction
Figure 1. RNA-seq of human term placenta (n=20)  
A) Circos diagram depicting whole-genome RNA-seq data
Comparative Proteomic Profile of the Human Placenta in Normal and Fetal Growth Restriction Subjects

Zhijing Miao, Min Chen, Hong Wu, Hongjuan Ding, Zhonghua Shi

1198 proteins
95 differentially expressed
Esp oxidative stress

Fig. 1. Schematic representation of network using Ingenuity pathway analysis (IPA) of differentially expressed genes. 35 of 95 total differentially expressed proteins are linked to two major molecular networks: erythropoiesis and oxidative stress which had the highest significant scores (A: hemoglobin network; B: nicotinamide adenine dinucleotide phosphate (NADPH) oxidase network). Relationships are defined in the legends. Green is indicative of genes going up and red depicts genes suppressed in the FGR placenta.
Variation in transcriptome

Evaluating intra- and inter-individual variation in the human placental transcriptome

David A. Hughes, Martin Kircher, Zhisong He, Song Guo, Genevieve L. Fairbrother, Carlos S. Moreno, Philipp Khaitovich and Mark Stoneking

Figure 8 Apportionment bar plot. Each gene was fit to a single model accounting for 13 explanatory variables and the proportion of variation explained by each variable was estimated using the sum of squares approach.
Around 70% of FGR has associated morphological placental pathology abnormalities.

MVM represents majority (50%) of FGR, esp early onset.

80+% of these are potentially detectable using USS assessment including Doppler studies, PLGF etc.
Some pathologies develop during pregnancy and unlikely to be identifiable pre-clinically, histology only (VUE, CHI, MPVFD...)

Around 25% of FGR, more late-onset, has no clear pathology correlates; may be amenable to future biochemical detection
Poor agreement regarding changes and poor correlation of morphology with clinical phenotypes for individuals

Placental examination contributes to categorisation and mechanistic grouping of FGR but is not gold standard for ‘pathology’

Future studies: clear phenotyping, blinded, objective assessments, relationship to functional (OMIC) features