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# Accepted Manuscript

Placenta Imaging Workshop 2018 report: Multiscale and multimodal approaches

Paddy Slator, Rosalind Aughwane, Georgina Cade, Daniel Taylor, Anna L. David, Rohan Lewis, Eric Jauniaux, Adrien Desjardins, Laurent J. Salomon, Anne-Elodie Millischer, Vassilis Tsatsaris, Mary Rutherford, Edward D. Johnstone, Andrew Melbourne, participants of the workshop



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# 1 Placenta Imaging Workshop 2018 Report: Multiscale and Multimodal Approaches

2

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4 Lewis<sup>6</sup>, Eric Jauniaux<sup>4</sup>, Adrien Desjardins<sup>2</sup>, Laurent J Salomon<sup>7</sup>, Anne-Elodie Millischer<sup>7</sup>,  
5 Vassilis Tsatsaris<sup>8</sup>, Mary Rutherford<sup>9</sup>, Edward D Johnstone<sup>10</sup>, Andrew Melbourne<sup>2,9</sup>,  
6 participants of the workshop\*.

7

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22 Manchester, UK.

23 \*Full list provided at the end of the article.

24

25 **Keywords:** Pregnancy, Placenta, Modelling, Multi-scale, Multi-modal, Collaboration

26

27 **Abstract:** The Centre for Medical Image Computing (CMIC) at University College London  
28 (UCL) hosted a two-day workshop on placenta imaging on April 12<sup>th</sup> and 13<sup>th</sup> 2018. The  
29 workshop consisted of 10 invited talks, 3 contributed talks, a poster session, a public  
30 interaction session and a panel discussion about the future direction of placental imaging.  
31 With approximately 50 placental researchers in attendance, the workshop was a platform  
32 for engineers, clinicians and medical experts in the field to network and exchange ideas.  
33 Attendees had the chance to explore over 20 posters with subjects ranging from the  
34 movement of blood within the placenta to the efficient segmentation of fetal MRI using  
35 deep learning tools. UCL public engagement specialists also presented a poster, encouraging  
36 attendees to learn more about how to engage patients and the public with their research,  
37 creating spaces for mutual learning and dialogue.

38

## 39 1. Organisation

40

41 *Organisers:* Paddy Slator, Rosalind Aughwane, Andrew Melbourne

42

43 *Speakers:* Anna David, Rohan Lewis, Eric Jauniaux, Adrien Desjardins, Laurent Salomon,  
44 Anne-Elodie Millischer, Vassilis Tsatsaris, Daniel Taylor, Romina Plitman Mayo, Gareth Nye,  
45 Simon Shah, Andrew Melbourne, Mary Rutherford, Ed Johnstone

46

## 47 2. Proceedings

48

49 **Anna David** opened the workshop on the first day by arguing *why we should image the*  
50 *placenta with MR* (Figure 1). The placenta's complexity as a dual circulatory system with an  
51 integral barrier between the mother and fetus(es) make it the most difficult organ to access  
52 in vivo. Great strides have been made in understanding the brain using magnetic resonance  
53 imaging. Now this technique is being applied to increase our understanding of placental  
54 structure and function. From a purely curious perspective the placenta is a fascinating organ  
55 that functions as a respiratory, renal, hepatic, endocrine, and vascular system for the  
56 developing fetus. The origins of the great obstetric syndromes of preterm birth, fetal growth  
57 restriction and pre-eclampsia probably come down to abnormal placental development and  
58 function. These conditions affect up to a third of all pregnancies and are a leading cause of  
59 neonatal and maternal morbidity and death globally. MR imaging of the placenta may shed  
60 light on the pathology of these complications as well as allow the response to novel  
61 treatments to be evaluated.

62

63 **Rohan Lewis** presented his group's work on *multiscale 3D imaging of the placenta*. These  
64 techniques allow identification of novel structures at the tissue, cellular and subcellular  
65 level, which are inaccessible using traditional 2D imaging techniques. Furthermore, the 3D  
66 approach demonstrates the spatial relationships between different features which allows  
67 relation of structure to function. The ability to see features and cellular spatial  
68 interrelationships that could not previously be visualised is leading to a new biological  
69 understanding of the placenta and may lead to novel biomarkers and therapeutic  
70 approaches.

71

72 **Eric Jauniaux** presented on *the etiopathology of ultrasound signs in the diagnosis of*  
73 *placenta accreta* and abnormally invasive placental disorders. Current findings continue to  
74 support the concept of a biologically defective decidua rather than a primarily abnormally  
75 invasive trophoblast. Prior caesarean section surgery increases the risk of placenta praevia  
76 and both adherent and invasive placenta accreta, suggesting that the endometrial/decidual  
77 defect following the iatrogenic creation of a uterine myometrium scar has an adverse effect  
78 on early implantation. Preferential attachment of the blastocyst to scar tissue facilitates  
79 abnormally deep invasion of trophoblastic cells and interactions with the radial and arcuate  
80 arteries. Subsequent high velocity maternal arterial inflow into the placenta creates large  
81 lacunae, destroying the normal cotyledonary arrangement of the villi.

82

83 **Adrien Desjardins** spoke on *photoacoustic and ultrasound imaging of the placenta*.  
84 Ultrasound imaging can be valuable to visualise the placenta for diagnostic and therapeutic  
85 procedures. However, current-generation ultrasound probes based on electronic  
86 components have several prominent limitations. For instance, they are unable to detect  
87 tissue colour directly, and it can be challenging to miniaturise them to the sub-millimetre  
88 scale for integration into minimally invasive devices. Optical methods for transmitting and  
89 receiving ultrasound are emerging as alternatives to their electrical counterparts. They offer  
90 several distinguishing advantages, including the potential to generate and detect broadband  
91 ultrasound required for high resolution imaging. The talk focused on recent work on  
92 photoacoustic imaging of the placenta, where ultrasound is generated in tissue using pulsed  
93 light, and fibre-optic generation of reception of ultrasound from within medical devices for

94 interventional imaging and medical device tracking. Adrien finally highlighted recent work  
95 on placental phantoms with tuneable optical, ultrasonic, and mechanical properties.

96  
97 *Functional MRI of the placenta* was the subject of **Laurent Salomon's** talk. Abnormal  
98 placentation is responsible for most failures in pregnancy. Functional MRI (fMRI) of the  
99 placenta has not yet been largely validated in a clinical setting, and most data are derived  
100 from animal studies. fMRI could be used to further explore placental functions that are  
101 related to vascularization, oxygenation, and metabolism in human pregnancies by the use of  
102 various enhancement processes: dynamic contrast-enhanced MRI, arterial spin labeling  
103 MRI, blood oxygen level-dependent and oxygen-enhanced as well as diffusion-weighted  
104 imaging and intravoxel incoherent motion MRI are various techniques that have been  
105 successfully applied to the functional imaging of the placenta. The ability of each fMRI  
106 technique to make a timely diagnosis of abnormal placentation that would allow for  
107 appropriate planning of follow-up examinations and optimal scheduling of delivery needs to  
108 be further investigated. Research programs will benefit from the use of well-defined  
109 sequences, standardized imaging protocols, and robust computational methods.

110  
111 **Anne-Elodie Millischer** presented work using *MRI with Gadolinium for the Diagnosis of*  
112 *Abnormally Invasive Placenta*. Ultrasound is the primary imaging modality for the diagnosis  
113 of placenta accreta, but it is not sufficiently accurate. MRI morphologic criteria have  
114 recently emerged as a useful tool in this setting, but their analysis is too subjective.  
115 Gadolinium enhancement may improve the accuracy to diagnose abnormal invasive  
116 placenta (AIP). Dynamic contrast gadolinium enhancement (DCE) MRI is emerging as a  
117 reliable procedure to diagnose AIP for both junior and senior radiologists. Particularly, the  
118 use of a specific pattern of enhancement, by allowing the extraction of tissular  
119 enhancement parameters, enables a predictable distinction between placenta accreta and  
120 normal placenta.

121  
122 **Daniel Taylor** presented on public engagement as a route to improving the quality and  
123 dissemination of research outcomes. There is increasing evidence to support this link, with a  
124 corresponding increase in funders' expectations of detailed plans as part of applications.  
125 However, there remain a number of perceived barriers across fields.

126  
127 These issues were discussed further at the poster session, where feedback demonstrated a  
128 clear appetite for public communication and involvement in this area. This is particularly  
129 timely given the clear link to patient impact and evidence of benefits, such as "lead(ing) to  
130 new research questions". There was also a clear perceived need to "reimagine the public  
131 image of the placenta". Despite this, many felt unsure of where to start, including which  
132 groups to target, methods of reaching them and how to access support. This correlates to  
133 national feedback in the Factors Affecting Public Engagement UK survey [1].

134  
135 Given the growing field there is increasingly institutional and local support available, with  
136 many universities, hospitals and biomedical research centres featuring teams to assist with  
137 developing activity. This is matched with national support such as the NCCPE [2], INVOLVE  
138 [3] and AHSNs [4], which are good starting points.

139

140 **Vassilis Tsatsaris** presented work undertaken in collaboration with **Edouard Lecarpentier**  
141 and **Olivier Morel** on *assessment of the utero-placental vascularization by ultrasound*  
142 approaches. The quality of utero-placental vasculature is essential for a proper fetal  
143 development and a successful pregnancy. Inadequate remodeling of the spiral arteries  
144 resulting in decreased maternal blood to the placenta has been implicated in the  
145 pathophysiology of preeclampsia and IUGR. However, the in vivo assessment of placental  
146 vascularization with non-invasive methods is complicated by the small size of placental  
147 terminal vessel, its complex architecture, and the very low blood velocities. Maternal utero-  
148 placental hemodynamics is currently assessed mainly by means of uterine artery  
149 pulsed Doppler, but this imaging modality has limited predictive value for preeclampsia and  
150 IUGR. Another approach consists in quantifying the vascularization directly in the placenta  
151 or the placental bed using a combined method of three-dimensional (3D) imaging and  
152 power Doppler ultrasonograph. First clinical studies suggest that the 3D power Doppler  
153 indices of the uteroplacental circulation could be helpful to improve the prediction of  
154 preeclampsia and IUGR. However, 3D power Doppler angiography of the placenta remains  
155 limited to large vessels and does not discriminate the fetal circulation from the  
156 maternal circulation. New technologies are emerging such as ultrafast scanners based  
157 on holographic imaging using unfocused ultrasonic waves. Recent studies suggest that  
158 ultrafast acquisition offers the possibility to analyze the flow with a high spatio-temporal  
159 resolution and may allow to discriminate maternal and fetal circulation.

160  
161 The second day of the workshop began with **Andrew Melbourne** presenting for **Rosalind**  
162 **Aughwane** on *MicroCT for imaging the human placenta*. Little is known about the three-  
163 dimensional structure of the fetoplacental vascular tree, due to the small size of vessels and  
164 complexity of branching structure. Micro-CT can capture this data in 3D volumes and opens  
165 a new window into our understanding of the vascular structure both in normal pregnancy  
166 and in major obstetric disorders including fetal growth restriction, pre-eclampsia and  
167 complicated twin pregnancies. MicroCT shows that there is substantial heterogeneity in  
168 vascular density within normal placentas, however some trends in the structure of the  
169 vascular tree appear to be conserved. The technique applied to the placenta allows the  
170 three-dimensional chorionic and deep branching vessel structure to be visualised and  
171 quantified, and can transform our understanding and appreciation of this much  
172 understudied but vital organ.

173  
174 **Mary Rutherford** gave an outline of the NIH-funded *Placenta Imaging Project*: the aim of  
175 this project is to develop an integrated MR approach to assess placental structure and  
176 function, and utilise it to characterise inadequate placentation. She then went on to discuss  
177 the links between placenta dysfunction and neonatal encephalopathy and perinatal brain  
178 injury.

179  
180 **Ed Johnstone** spoke about *paying attention to the placenta to improve antenatal care*:  
181 during pregnancy monitoring attention is understandably focused on the fetus and the  
182 mother. However, the placenta sits at the interface between the two and examining it is  
183 essential if we are to gain a full picture of pregnancy health and well-being. Traditionally,  
184 antenatal placental assessment has primarily been confined to determining placental  
185 location, but more recently attention has focused on trying to gauge and measure placental  
186 function and health in vivo, particularly in pregnancies at risk of poor outcomes. The

187 presentation discussed how his group are using imaging technologies to influence antenatal  
188 care and improve outcomes, how studies using ultrasound, magnetic resonance imaging  
189 and microCT will continue to expand the importance of examining the placenta in clinical  
190 care, and where he perceived the next important advances need to occur.

191

### 192 **3. Panel Discussion**

193

194 The final session of the workshop was a panel-led discussion on the future direction of  
195 placenta imaging research.

196

197 The discussion was led by Anna David, Mary Rutherford and Ed Johnstone, with many  
198 contributions from the audience. Figure 2 shows a mind map highlighting important  
199 outcomes collected on a white board during the discussion. Several key themes emerged  
200 throughout our panel discussion:

201

202 **Collaboration** – through coordinated research effort between Centres we can maximise the  
203 sharing of methods and data between research groups. A coordinated effort to make  
204 standardised imaging data available would help researchers share ideas and avoid  
205 replication. Funding would be needed to support this initiative. A central agreed registry of  
206 data is one possible solution; Ed Johnstone offered to investigate if the Tommy's MRC  
207 biobank was prepared to host a national or international dataset of placental MRI. The  
208 placentome.org webpage, which is particularly relevant for modelling work, may represent  
209 the first step towards this.

210

211 **Outreach** – more is needed to communicate the importance of the placenta, and better  
212 understanding of its importance for future maternal and fetal health. Increasing public  
213 education and understanding will help boost recruitment, and hopefully lead to more *ex*  
214 *utero* placentas available for study *ex utero* after birth. Families will be more likely to donate  
215 placentas if they understand the importance of the organ and the potential benefits of  
216 placental examination and research to future pregnancies.

217

218 More **Research** into placental pathology is needed to understand the broad spectrum of  
219 placental conditions and fetal compensation in response to poor placentation. Pre-  
220 pregnancy imaging and correlation with subsequent placentation is likely to be a key  
221 research area, but is yet to be studied in detail. Very early imaging of pregnancy is also likely  
222 to become more important, with aims of establishing the timing of future intervention, and  
223 helping provide early prediction of outcome.

224

225 **Imaging** is vital for improving our understanding of placental physiology and efficiency.  
226 Current techniques are beginning to help us understand flow matching, and what  
227 constitutes a functional placenta. Many **new techniques** are emerging with much potential  
228 for advancing our understanding of the placenta: these include perfusion imaging,  
229 computational modelling of the placenta, placenta MR spectroscopy, and arterial spin  
230 labelled MRI. But these techniques currently have limitations due to difficulties with  
231 reproducibility, and more is needed regarding future protocol development. Automatic  
232 placental image analysis tools such as automated segmentation will be critical to future  
233 large-scale studies. Future projects will need to explore the value of these new imaging

234 techniques and standardise measurements across hardware, software, and populations.  
235 Work on correlative imaging between modalities and between scales is an important area  
236 for future work. Mappings between different imaging modalities will be useful, since some  
237 imaging techniques have clear advantages in terms of cost, comfort or safety.

238

239 **Motion** remains an unsolved problem especially in MRI, complicated by the presence of  
240 mechanical vibration and reports of uterine contractions.

241

242 **Maternal position** remains a point of interest for MRI scans; there are valid, evidence-based  
243 concerns about compression of the vena cava during supine scanning. Ongoing efforts aim  
244 to evaluate if a supine position may offer greater consistency across scans, without  
245 compromising patient safety and comfort compared to left- or right- lateral positions.

246

247 In particular, **standardising inclusion criteria and data collection** for women with  
248 pathological pregnancies is vital to allow comparison of placental imaging findings between  
249 studies. Attention must be paid by researchers to ensure that characteristics such as  
250 maternal blood pressure and the timing of anti-hypertensive treatment is documented in  
251 relation to scans, as these factors may affect the results.

252

253 **More imaging** is needed, both in vivo and ex vivo. Longitudinal imaging is desirable. For  
254 large scale studies, long term follow-up is essential with precise definition of outcome at all  
255 stages. Focus is needed on the most important outcomes for each pathology. Birth weight is  
256 a useful proxy outcome, but the real goal should be to monitor the long-term health of  
257 children, ideally until school age. There are imminent core outcome sets for fetal growth  
258 restriction as part of an ongoing study and similar sets will need to be defined for other  
259 placental pathologies.

260

261 The discussion ended with some thoughts for the future and our hope to meet again next  
262 year.

263

#### 264 **4. Summary**

265 This workshop at UCL showcased many aspects of research into the placenta across multiple  
266 scales and multiple imaging modalities. What is clear is that the future holds much promise  
267 for this much under-studied organ and future collaborations and sharing of data between  
268 groups will surely be extremely productive. We hope that the recent drive to publish the  
269 proceedings of placental workshops (e.g. [5]) will stimulate broader collaboration and  
270 deeper discussion of the common issues surrounding our shared research interests.

271

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275 US National Institutes of Health (grant 1U01HD087202-01).

276

#### 277 **References**

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280 (<https://www.publicengagement.ac.uk>)



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282 and social care research (<http://www.invo.org.uk>)
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291 15.

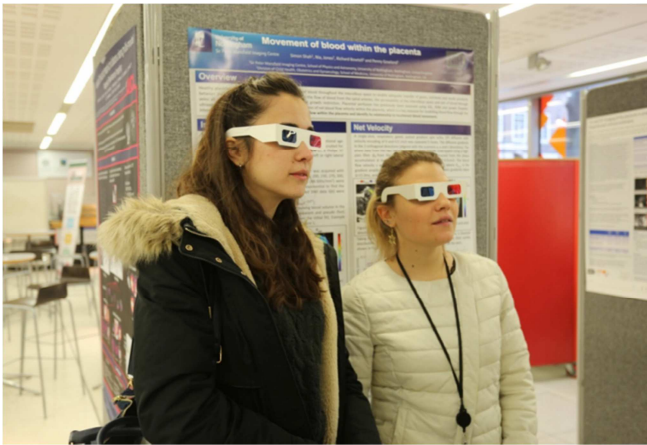
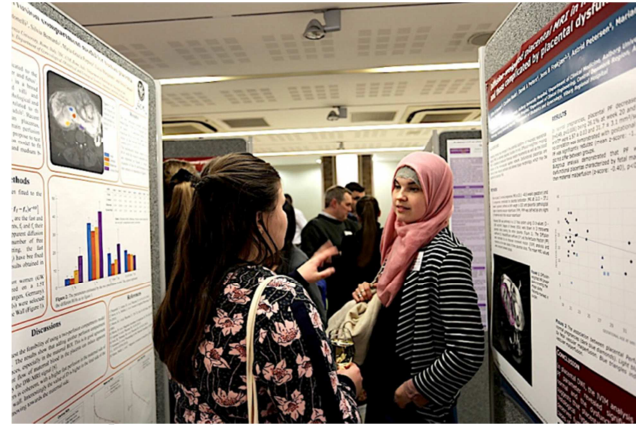
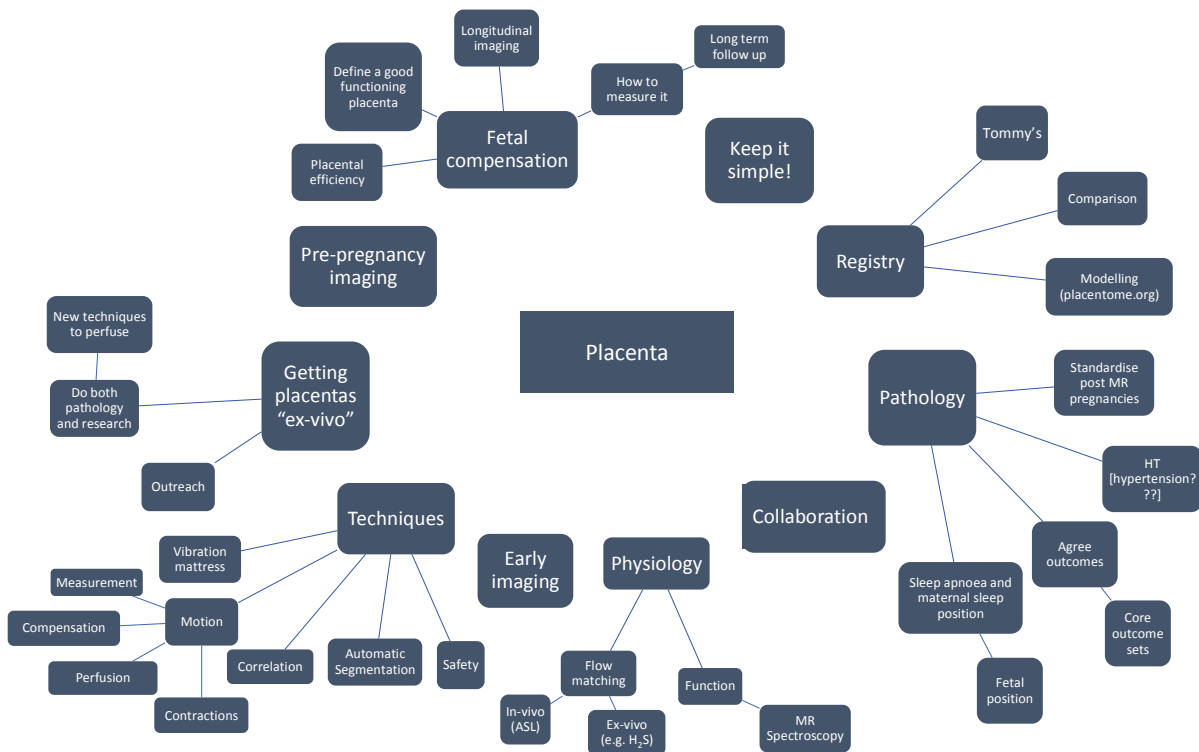


Figure 1: Photo montage from the 2018 Placenta Imaging Workshop

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341



342

343 **Figure 2: Mind map arising from panel discussion on the future direction of placenta imaging research.**

344

345 **Full List of Workshop Participants**

346 David Atkinson, Rosalind Aughwane, Rupanjali Baranikumar, Charline Bertholdt, Elisenda  
 347 Bonet-Carne, Paul Brownbill, Paul Brownbill, Muriel Bruchhage, Richard Caulfield, Igor  
 348 Chernyavsky, Andrew Chew, Anna David, Adrien Desjardins, Enrico De Vita, Tom Doel,  
 349 Alexander Erlich, Dimitra Flouri, Michele Guerreri, Matina Hakim, Ditte Hansen, Makinah  
 350 Haq, Parvez Haris, Sara Hillman, Alison Ho, Jana Hutter, Laurence Jackson, Eric Jauniaux,  
 351 Edward Johnstone, Esra Kipergil, Silvia Labianco, Rohan Lewis, Christina Malamateniou,  
 352 Efthymios Maneas, Andrew Melbourne, Anne-Elodie Millischer, Enrique Monton, David  
 353 Morris, Julie Nihouarn, Gareth Nye, Helen O'Neill, Mette Østergaard Thunbo, Marco  
 354 Palombo, Rachel Peasley, Kelly Pegoretti Baruteau, Romina Plitman Mayo, Saskia Port, Mary  
 355 Rutherford, Laurent Salomon, Simon Shah, Paddy Slator, Natalia Soe, Anne Soerensen,  
 356 Magdalena Sokolska, Carla Svigilsky, Teresa Tropea, Vassilis Tsatsaris, Guotai Wang, Bilal  
 357 Yassine

358

- Summary of the Centre for Medical Image Computing Placenta Imaging Workshop 2018
- Talks covered multiscale and multimodal imaging techniques
- Panel discussion on the future of placental imaging research
- Discussion of placenta-specific public engagement issues

ACCEPTED MANUSCRIPT