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Placenta Imaging Workshop 2018 report: Multiscale and multimodal approaches

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1 **Placenta Imaging Workshop 2018 Report: Multiscale and Multimodal Approaches**
2

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24

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 12th and 13th 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

Organisers: Paddy Slator, Rosalind Aughwane, Andrew Melbourne

42

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 surroundings our shared research interests.
271

276

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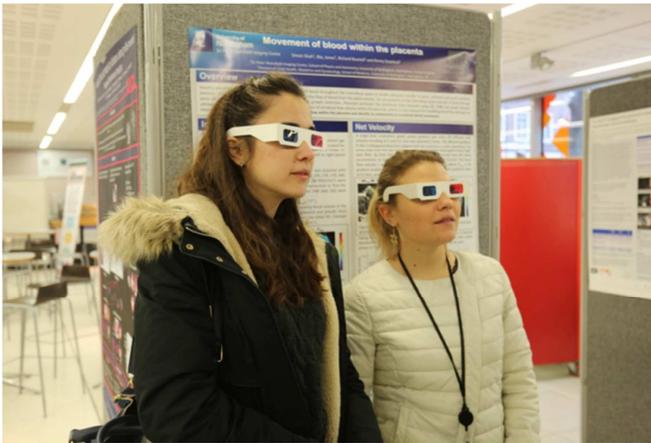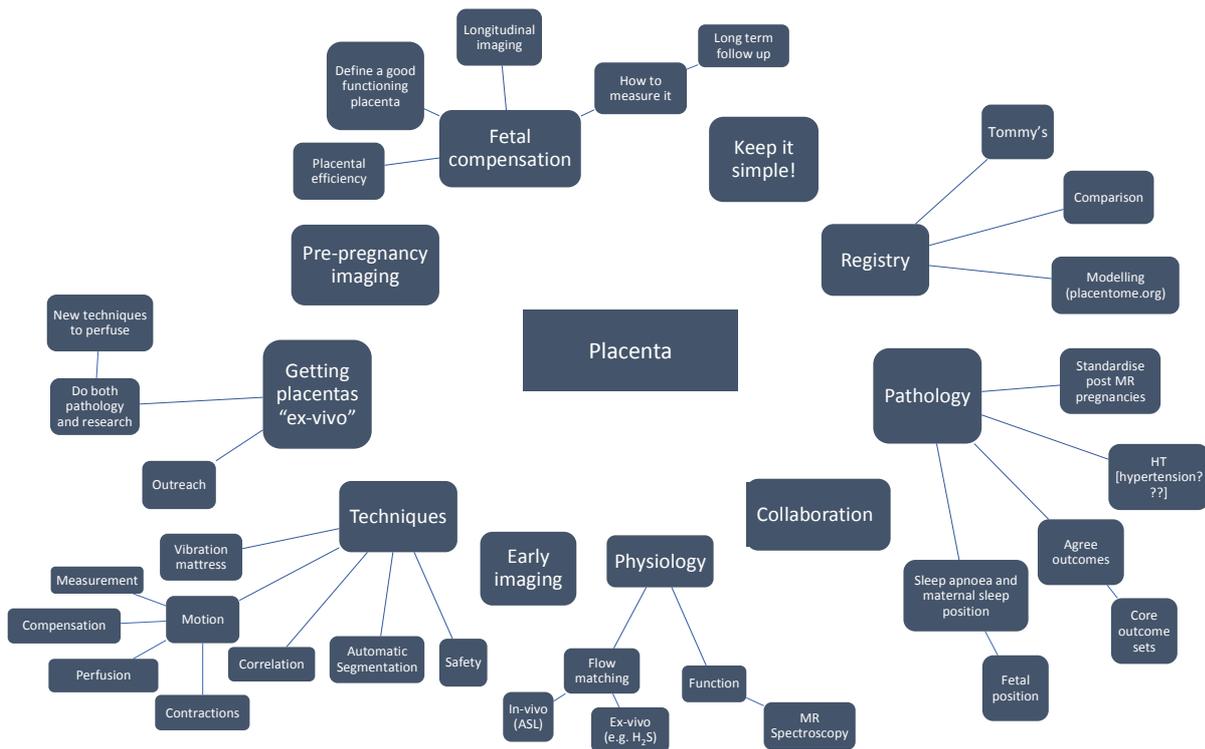290 Placenta. 2018 Apr;64 Suppl 1:S4-S8. doi: 10.1016/j.placenta.2017.12.011. Epub 2017 Dec
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Figure 1: Photo montage from the 2018 Placenta Imaging Workshop

341

342

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

344

Full List of Workshop Participants

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- 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