IFPA Meeting 2017 Workshop Report: Clinical placentology of stillbirth, 3D structure-based modelling of placental function, placental bed, and treating placental dysfunction

John Aplin, University of Manchester, UK

Paul Brownbill, University of Manchester, UK

Judith Bulmer, Newcastle University, Australia

Graham Burton, Cambridge University, UK

Larry Chamley, University of Auckland, New Zealand

Igor Chernyavsky, University of Manchester, UK

Alys Clark, University of Auckland, New Zealand

Elizabeth Cottrell, University of Manchester, UK

Anna David,

Mark Dilworth, University of Manchester, UK

David Elad, Tel Aviv University, Israel

Linda Ernst,

Marcel Filoche, École Polytechnique, France

Natalie Hannan, University of Melbourne, Australia

Alexander Heazell, University of Manchester, UK

Sebastian Illanes

Oliver Jensen, University of Manchester, UK

Ed Johnstone, University of Manchester, UK

Lopa Leach, University of Nottingham

Samantha Lean,

Michal Levy,

Rohan Lewis, University of Southampton, UK

Terry Morgan, Oregon Health and Science University, USA

Gareth Nye, University of Manchester, UK

Michelle Oyen, University of Cambridge, UK

Carolyn Salafia, Placental Analytics Llc, USA

Henning Schneider, University of Bern, Switzerland

Gitta Turowski

Perrie O'Tierney-Ginn, Center for Reproductive Health, MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio, USA

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Address for correspondence: Dr. Perrie F O'Tierney-Ginn

Center for Reproductive Health

MetroHealth Medical Center

2500 MetroHealth Drive, R358

Cleveland, Ohio, USA 44109

Email: poginn@metrohealth.org

Phone: 1-216-778-8983

Fax: 1-216-778-8282

Abstract

Workshops are an important part of the IFPA annual meeting as they allow for discussion of specialized topics. At IFPA meeting 2017 there were four themed workshops, all of which are summarized in this report. These workshops discussed new knowledge and technological innovations in the following areas of research: 1) placental bed; 2) 3D structural modelling; 3) clinical placentology of stillbirth; 4) treatment of placental dysfunction.

1 3D structure-based modelling of placental function

Chairs: Paul Brownbill, Igor Chernyavsky, Alys Clark, Oliver Jensen, Ed Johnstone, Lopa Leach, Rohan Lewis, Carolyn Salafia, Henning Schneider

Speakers: Alys Clark, David Elad, Marcel Filoche, Rohan Lewis, Michelle Oyen, Gareth Nye

1.1 Outline

The workshop comprised of three synergistic parts, each followed by interactive discussion: (i) placental imaging, accounting for state of the art three-dimensional microscopy; (ii) human placenta physiology relating to blood flow and oxygen transfer; (iii) advances in human placental mathematical modelling predicting transfer and blood flow based on placental structural morphology.

1.2 Summary

In the first section on “Structure”, **Rohan Lewis** introduced multi-scale 3D imaging of placental villi as the basis for modelling and functional analysis. It was described how the three-dimensional structure of the placental villi and the complex spatial relationships of the cells they contain are central to placental function. Multi-scale imaging techniques including micro-CT, whole-mount confocal, light sheet and serial block-face scanning electron microscopy now allow three-dimensional imaging of whole placentas or regions of placenta down to the nm scale. There was an illustration of how these approaches can inform computational and molecular studies and advance our understanding of placental function. Discussion centered on pericyte associations with the endothelium; and potential future insight into the true meaning

of syncytial knots, given the high-resolution imaging that is now possible at the microvillous surface.

In the second section on “Function”, **David Elad** showed how the *ex vivo* human placental perfusion model could be used in a single (fetal) side perfusion adaptation to analyze resistance indices in the feto-placental chorionic plate vasculature with Doppler. The efficacy of material exchange in the human placenta depends on proper blood perfusion through the complex 3D branching network of the feto-placental vasculature. Accordingly, obstetrics monitoring guidelines have evolved based on clinical studies that explored correlations between umbilical Doppler indices and pregnancy outcome. However, the biophysical foundation is vague and only based on simplified lumped element models of electronic circuits without experimental validations. David and his co-workers have developed an *ex vivo* placental perfusion model to study placental insufficiency by exploring the dependency of umbilical Doppler indices on obstruction levels of major fetal vessels in the chorionic plate. There was some discussion on interpretation of values in relation to the resistance from the underlying microcirculation. The context of the study was also explained, as this was a single-sided perfusion model, which only explored feto-placental vascular resistance.

Continuing with the “functional” theme, **Gareth Nye** presented a new method to probe oxygen transfer function in the human placenta *ex vivo*. Fetal growth restriction (FGR) is associated with reduced placental functional capacity, including compromised oxygen transfer. However, there is little information on placental oxygenation *in vivo* and its correlation with flow and structure. In this talk, Gareth discussed a novel approach to assess oxygen transfer dynamics *ex vivo* in a dually perfused human placenta that involves measuring both the net oxygen transfer rate and

systematic mapping of oxygen levels in the intervillous space. This methodology could allow bridging the gap between the structure and function in health and FGR, forming the basis for validation of placenta-specific computational models. There was discussion on how the *ex vivo* human placental perfusion model has seen numerous variations, relating to different research questions. In this instance the single maternal-side cannula was defended, in an aim to simplify the system for the purposes of low flow interference during 3D tissue mapping of pO_2.

Moving onto engineering and modelling approaches in the "Integration" section, **Alys Clark** spoke on "How can computational models of the placenta be used to guide diagnostics?" Computational models of placental function are often used to provide insight into the efficiency of the placenta in normal and abnormal development. Advances in imaging technologies and computational power are allowing predictive models of the placenta to be developed with ever increasing anatomical detail. This opens the door for development of models that can begin to be used, in conjunction with imaging, to guide diagnostics and therapies. Alys discussed computational models of the placenta in the context of models that have successfully bridged the gap between physiology and the clinic, and challenges for the future. There was discussion on how we should interpret drug effects on transfer function and their effects on resistance to fetal blood flow. Also, how changes in patient treatment strategies might be assisted by modelling of the placenta, with a comparison on how models could be used to predict effects of changes in lung ventilation. The appeal from the bioengineers and modelers to clinical scientists is "what are the big questions that need to be addressed in their work." Answering the wrong questions can be wasteful in terms of their translational efforts.

This talk was followed by **Michelle Oyen**, who presented the question “How do we validate virtual placenta models?” There has been significant recent interest in, and progress in, the area of computational modelling of the human placenta in pregnancy. However, the thorny question of how to validate those models has no easy or obvious solution. The use of *in silico* studies for human pregnancy has obvious ethical advantages over any experimental study involving pregnant women. However, without validation the models are “garbage in, garbage out” exercises where the quantitative results could mean anything. This talk highlighted the key issues and challenges going forward towards a functional virtual placenta model that is useful for clinical and research understanding. Technicalities were explored during the discussion, of how in the finite element model, the whole picture is broken down into parts, e.g. how fetal capillary tortuosity affects fetal blood flow; how inflow rates to a network affects the flux of oxygen across the placental barrier. Modelling efficacy means little without the processing of quality data, including sufficient slice sampling during structural reconstruction and without too much error in meshing data.

In the final talk, **Marcel Filoche** spoke about the role of morphology in mathematical models of placental gas exchange. One of the main functions of the human placenta is to transfer oxygen from maternal to fetal blood. To assess its performance as a gas exchanger, mathematical and numerical models must account for the physiology of exchange and organ morphology. Recent progress in imaging permits the extraction of detailed morphological information, which can be used as input for these models. Marcel presented an overview of the gas exchange models in the placenta, discussing their advantages and shortcomings. He showed how geometrical information can improve our understanding of the working of the placenta, and suggested

future approaches based on the latest experimental techniques. Discussion ensued on knowing the geometry of what is being examined and knowing what questions are being asked in relation to this. The need to understand flow around complex geometric shapes, i.e. the villous tree and the prospect of setting agreed upon international standards was raised. From a pathologist's perspective, the most vexing questions would relate to stillbirth and the need to work this into experimental and modelling investigations; relating to this, which measurements should be performed? We should consider that materno-placental flow probably does not cover the entire villous surface simultaneously; there is a functional dynamic here. The rheology of blood flow was discussed, being different in the maternal intervillous space, compared to the vascularized feto-placental circulation.

With such a vast array of questions that could be asked, **Igor Chernyavsky** closed the workshop by highlighting the importance of establishing the standards for emerging experimental techniques, computational models' validation and data sharing to allow for more quantitative and direct inspection of structure-function interaction in the human placenta than ever before.

1.3 Conclusions

Placental modelling has been conducted over many decades relating to heat, nutrient and water exchange across the placental barrier. More recently, technical advances in microscopy and other imaging techniques have led to several groups taking serious attempts to couple structure with function, using mathematical modelling. The *ex vivo* dual perfusion of the human placenta and other *in vitro* human placental techniques are also being developed in parallel and provide rich means of validation for computational models in predicting the outcomes for placental

transfer and placental oxygen consumption. This research direction is vital in considering placental pathology, where placental architecture and blood flow relationships diverge from normality in a non-trivial way. The interdisciplinary placenta community is thus at a juncture of developing some important modelling tools for use by obstetricians, in combination with advanced *in vivo* imaging, to help predict and manage problem pregnancies, including fetal growth restriction.