Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in
Biomedical Engineering

Micro-haemodynamics at the maternal–fetal interface: Experimental, theoretical and clinical perspectives

Qi Zhou[1,a], Eleanor Doman[2,a], Kerstin Schirrmann[3,4,a], Qi Chen[3,4], Elizabeth A. Seed[1], Edward D. Johnstone[5,6], P. Ravi Selvaganapathy[7], Anne Juel[3,4], Oliver E. Jensen[2], Miguel O. Bernabeu[8,9], Timm Krüger[1] and Igor L. Chernyavsky[2,5]

Abstract

The placenta is a vital interface between the mother and her developing fetus. Micro-haemodynamics of the placenta, where the particulate nature of blood flow cannot be ignored, mediates the relationship between the organ's structure and its function. However, the placenta's complex architecture and its relation to pregnancy pathologies remain poorly understood. This review covers current challenges in characterising placental micro-haemodynamics. Recent progress in three-dimensional multi-scale imaging has stimulated the development of image-based theoretical models, but existing approaches do not fully harness the available data, and new tools are needed for the assimilation of complex imaging datasets. Although the placenta at term is available for *in vivo* imaging or *ex vivo* experimentation, insight into placental micro-rheology is limited, necessitating the use of biomimetic models. Microfluidic approaches offer opportunities for well-controlled characterisation of micro-rheology in complex geometries, but challenges remain in the robust fabrication of these systems. Recent advances in high-performance simulations for suspension flows enable parametrisation of key physical processes at the micro-scale. Future progress can be made by optimising computational architecture and integrating micro-haemodynamics with solute transport. Both experimental and computational approaches require translation to the organ scale. New upscaling approaches will need to accommodate non-local interactions in microvascular network flows and address the lack of clear scale separation across the placental architecture. Together, recent advances in cross-disciplinary imaging and modelling over the last ten years have opened a pathway for an *in silico* human placenta, accelerating the development of precision obstetrics medicine in the next decade.

Addresses

[1] School of Engineering, Institute for Multiscale Thermofluids, The University of Edinburgh, Edinburgh, EH9 3FB, UK
[2] Department of Mathematics, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK
[3] Manchester Centre for Nonlinear Dynamics, The University of Manchester, Manchester, M13 9PL, UK
[4] Department of Physics and Astronomy, The University of Manchester, Manchester, M13 9PL, UK
[5] Maternal and Fetal Health Research Centre, School of Medical Sciences, The University of Manchester, Manchester, M13 9PL, UK
[6] MAHSC, St Mary's Hospital, NHS MFT, Manchester, M13 9WL, UK
[7] Department of Mechanical Engineering, School of Biomedical Engineering, McMaster University, Hamilton, Ontario, L8S 4L7, Canada
[8] Centre for Medical Informatics, Usher Institute, The University of Edinburgh, Edinburgh, EH16 4UX, UK
[9] The Bayes Centre, The University of Edinburgh, Edinburgh, EH8 9BT, UK

Corresponding author: Chernyavsky, Igor L (igor.chernyavsky@manchester.ac.uk)
[a] Joint first authors. These authors contributed equally to the work.

Current Opinion in Biomedical Engineering 2022, **22:**100387

This review comes from a themed issue on **Futures of BME 2022: Bioengineering for Women's Health**

Edited by **Nimmi Ramanujam**

For complete overview of the section, please refer the article collection - Futures of BME 2022: Bioengineering for Women's Health

Received 16 August 2021, revised 17 October 2021, accepted 16 March 2022

https://doi.org/10.1016/j.cobme.2022.100387

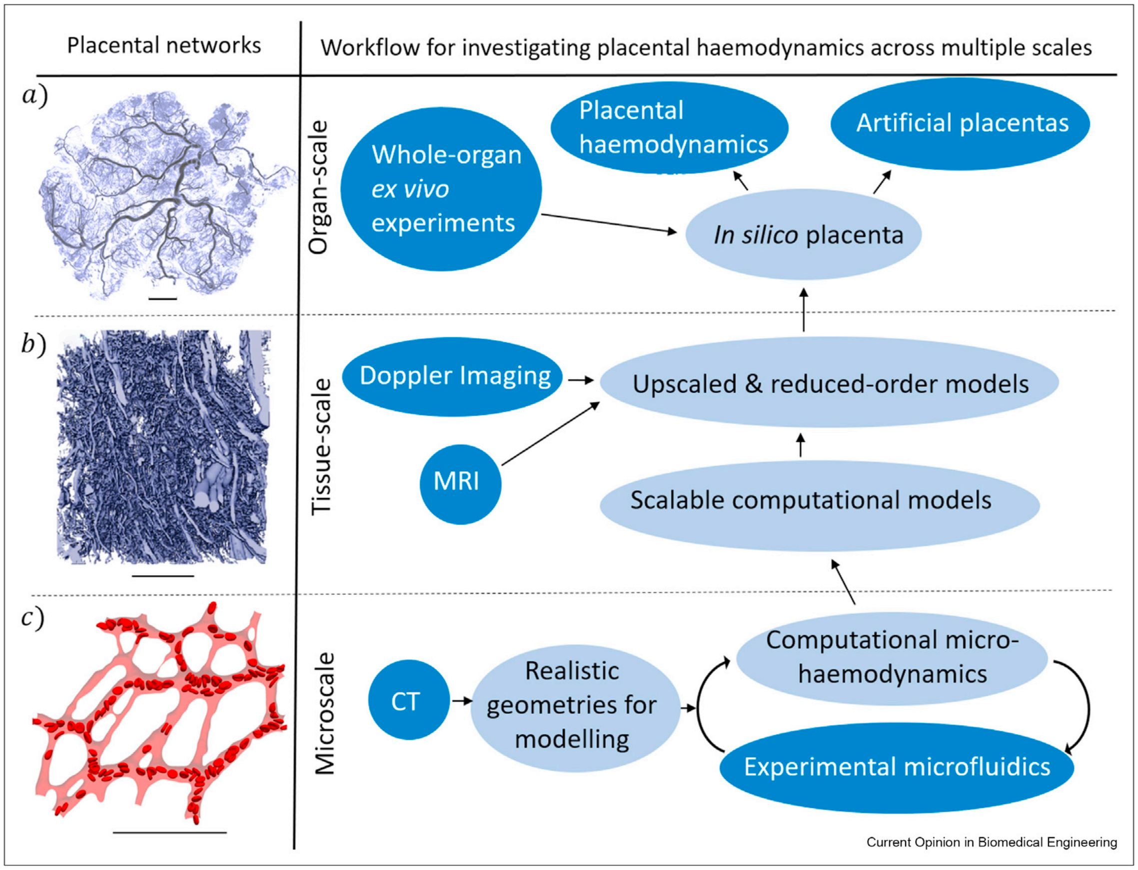
Keywords
Human placenta, Artificial placenta, Imaging, Haemodynamics, Microfluidics, Computer simulations, Upscaling.

Micro-haemodynamics in normal and complicated pregnancy

The healthy development of a fetus critically depends on the maternal–fetal interface provided by the human placenta [3]. During gestation, the placenta rapidly develops into a densely packed solute-exchange system with a large surface-area-to-volume ratio [4] (Figure 1). The maternal uterine circulation delivers nutrients and removes waste products via a heterogeneous porous placental space (also known as the *intervillous space*, IVS; Figure 2a) interfaced with the feto-placental vascular tree (Figure 1a,b), which is itself linked to the fetus via the umbilical cord.

Maternal and fetal components of the human placenta need to work synergistically to balance its multiple

Figure 1



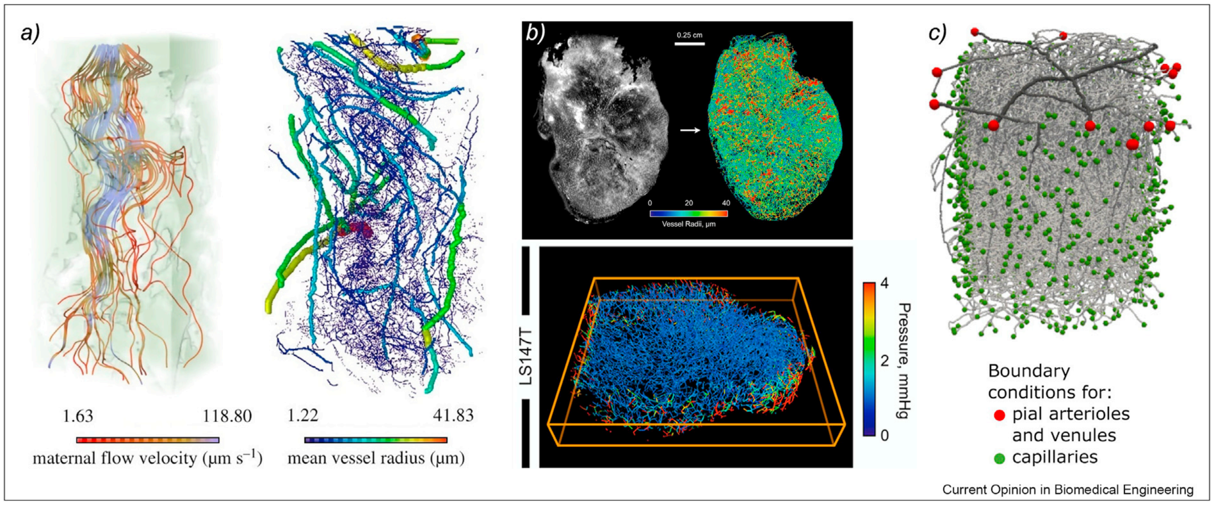
Workflow for biomimetic modelling of the micro-haemodynamics in the human placenta. Dark blue bubbles refer to experimental methods and light blue bubbles refer to theoretical methods. (**a**) Whole-organ synchrotron micro-CT showing the fetal placental vasculature (scale bar: 25 mm; reproduced from Ref. [1]). (**b**) Segmented feto-placental vascular network from synchrotron micro-CT image (scale bar: 500 μm; reproduced from Ref. [1]). (**c**) Computational simulation of red blood cells flowing through realistic microvascular networks (scale bar: 100 μm; reproduced from Ref. [2]). All images reproduced under CC BY 4.0. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

functions, such as the robust exchange of a diverse range of solutes. In particular, the transport of oxygen and carbon dioxide is strongly facilitated by the haemoglobin of the red blood cells (RBCs) and thus depends on adequate distribution of local *haematocrit* (the volume fraction of RBCs) [5]. Micro-haemodynamics of the placenta, where the particulate nature of blood flow cannot be ignored (Figure 1c), mediates the relationship between the organ's structure and its function. However, the role of placental architecture in pregnancy pathologies remains poorly understood, and multiple biological factors, such as oxidative- and mechanical-stress-induced damage [6], are associated with inadequate micro-haemodynamics.

Pathologies of the human placenta and the role of micro-rheology

Many pregnancy complications are associated with impaired placental micro-haemodynamics and associated pathophysiology [3,6–8]. In normal pregnancy, the shear stress at the materno-placental interface (trophoblast syncytium) is estimated to be $\lesssim$ 1 Pa [4], which illustrates that in the healthy placenta, the materno-placental IVS pore space operates as a low-resistance and low-pressure flow system [3]. The endothelium in feto-placental villous capillaries is predicted to face shear stresses of a similar order of magnitude [5]. Notably, both placental interfaces are characterised by considerable spatial heterogeneity [4,5]. *Pre-eclampsia* and *fetal growth restriction* (FGR), highly prevalent pregnancy disorders, are often accompanied by elevated blood pressure and flow velocities in the materno-placental IVS [3,9]. On the other hand, the feto-placental tree and corresponding vascular network are often smaller, with less developed branching structure, in severe FGR and pre-eclampsia than in normal pregnancy, therefore increasing the resistance to fetal blood flow [6]. Both structural alterations result in an environment of high mechanical stress that increases the chance of RBC *lysis* (disintegration, associated with the release of toxic cell-free haemoglobin [8,10]) and

Figure 2



Assimilation of complex biological geometries into computational models. (**a**) Three-dimensional flow through the maternal intervillous porous space (IVS; left) embedded in the fetal vascular network (right) of human placental tissue (reproduced from Ref. [1]). (**b**) Image segmentation (top) and intravascular pressure analysis (bottom) of human colorectal carcinoma xenograft (reproduced from Ref. [22]). (**c**) Hierarchical boundary conditions applied to the microvascular networks of mouse parietal cerebral cortex (reproduced from Ref. [23]). All images reproduced under CC BY 4.0.

damage to the endothelial or syncytial trophoblast cellular linings in FGR placentas (as observed in other micro-haemodynamical systems [11]).

In normal pregnancy, the growing demand of the fetus has to be balanced with maternal circulatory capacity and protection against adverse haemodynamical events for the mother and her placenta. While the production of maternal RBCs is increased during gestation, the maternal haematocrit and overall haemoglobin content per blood volume are reduced [8,12]. At the same time, the volume of each RBC and its haemoglobin content are slightly elevated, resulting in a more spherical shape. This makes maternal RBCs potentially more susceptible to osmotic stress damage, further evidenced by *microcytosis* (reduced RBC volume and haemoglobin content) in pre-eclampsia as a potential adaptive response [8]. Similarly, reduced placental oxygen supply at abnormally low maternal haematocrit and/or haemoglobin levels, such as in the case of maternal *anaemia* (iron deficiency), could be partly compensated by placental hypertrophy and increased feto-placental vascularisation [12].

A related set of conditions known as *haemoglobinopathies*, for example, *sickle-cell* disease, also strongly impact the micro-rheology of the placental blood flow. The altered shape and mechanical properties of RBCs increase the incidence of IVS occlusions, haemolysis, hypoxia and associated pathophysiology [13].

The structure of placenta in *diabetic* patients (including gestational, Type I and Type II diabetes mellitus) can often be altered in a way that is radically different from pre-eclampsia, while still leading to FGR. In particular, the materno-placental IVS is less sparse in diabetes than in normal (and much less than in pre-eclamptic) placental tissue, while the feto-placental network is less mature but more hyper-vascularised at the exchange interface [7]. Future studies should further evaluate the relative contributions of altered placental micro-architecture, RBC shape and mechanical properties to the pathophysiology of placental haemodynamics and solute transport.

The need for biomimetic *in vitro* and *in silico* models

To facilitate early diagnosis of developing placental dysfunction during pregnancy, a mechanistic understanding of the relationship between placental structure and function is required, which is mediated by micro-haemodynamics at the intricate maternal–fetal interface [14]. Despite recent progress in advanced three-dimensional (3D) microscopy of placental architecture (Figure 1b), current clinical *in vivo* imaging and physiological *ex vivo* perfusion experiments lack the resolution needed for functional assessment of the placental micro-haemodynamical environment [15]. The high evolutionary divergence of placental anatomy and physiology makes common animal models (e.g., mouse, rat and sheep) unsuitable for reliable inferences about the human placenta [16], and the use of non-human primates is largely inaccessible due to ethical and cost considerations. However, emerging rich imaging datasets pave the way to advanced biomimetic modelling, either *in vitro* or *in silico*, which allows for exhaustive testing of hypotheses regarding the interplay of placental microstructure and micro-haemodynamics [15].

Assimilating complex heterogeneous geometries into models

To develop biomimetic models of placental micro-haemodynamics, we must first establish robust and efficient workflows to register and characterise representative tissue geometries.

Robust segmentation and characterisation of micro-geometry for image-based modelling

The human placenta presents a unique challenge as a highly heterogeneous and dynamic organ, requiring massively multiscale and multi-modal imaging to quantify its function [17,18]. Additionally, the feto-placental vascular space, materno-placental IVS and the villous tissue barrier comprise three distinct domains which must be distinguished within imaging modalities for accurate reconstruction of placental micro-architecture. Progress has been made recently using *ex vivo* synchrotron X-ray tomography with novel contrast agents or *in vivo* MRI techniques, in combination with machine-learning-based segmentation algorithms, such as U-net [1,19]. Multiple challenges, however, remain in the robust preparation of samples that preserve their 3D morphology and in quality-assured and efficient structural image analysis that accurately captures geometrically complex maternal and fetal placental domains.

Characterisation of placental microstructure, once obtained, is another challenge shared with other complex heterogeneous disordered media. A combination of topological data analysis, spatial probability and statistical physics approaches enables increasingly deep insights into the role of microstructural fluctuations for flow and transport in disordered porous media [20] or networks [21]. Nevertheless, much remains unknown about robust and optimal strategies for identifying representative volumes of placental tissue, given its heterogeneity and markedly different spatial scales of the maternal and fetal placental domains [1]. Future progress in computational modelling and biomimetic microfluidics will be enabled by generating more accurate synthetic porous media and vascular networks that match statistically the placental geometry.

Tackling boundary condition uncertainty in micro-haemodynamical models

Even with the accurate characterisation of the placental microstructure, micro-haemodynamical models depend strongly on tissue-scale boundary conditions, which are often uncertain. Furthermore, the two principal circulatory domains in the human placenta, the maternal IVS and the fetal villous capillary networks, require different modelling approaches. For the former, blood flow in a heterogeneous IVS can be modelled by assuming a tissue-scale pressure gradient [1] (Figure 2a). For the latter, boundary conditions at network inlets and outlets need to be prescribed iteratively to match physiological ranges for blood pressure, haematocrit and wall shear stress, borrowing modelling approaches from other biological networks, such as vascular tumours [22] and cerebral cortex [23] (Figure 2b,c).

In both domains, the model boundary conditions and physiological target ranges rely on *in vivo* or *ex vivo* measurements, with their associated uncertainties, arising from individual and regional variability due to the inherent heterogeneity of placental microstructure and the resolution limit of measurement protocols [15,24]. Coupling the two circulatory domains across a complex placental barrier also presents many open challenges. In particular, future models will need to address capillary- and pore-scale boundary conditions due to passive, facilitated and active transport of solutes at the villous syncytial and endothelial sides of the barrier, which are likely to be spatially varying and solute-specific [4].

Box 1. Key challenges in placental micro-haemodynamics.

- *Microstructure*: Robust and efficient experimental and computational pipelines are needed for sample preparation, imaging, segmentation and statistical characterisation.
- *Boundaries*: Physiological boundary conditions must be extracted at the tissue level, accounting for RBC−RBC and RBC−surface (in particular, the syncytial microvillous surface) interactions.
- *Microfluidics*: New experimental methods are needed for the micro-fabrication of biomimetic capsules and complex three-dimensional micro-architectures.
- *Simulations*: Cell-scale flow and transport simulators must be integrated and optimised, with respect to spatio-temporal decomposition and hybrid GPU/CPU parallelisation.
- *Reduced-order modelling*: New mathematical models are needed for nonlinear and non-local transport in disordered networks and porous media.
- *Clinical imaging*: Tissue-scale haemodynamics must be linked to MRI and Doppler ultrasound physics, accounting for local haematocrit heterogeneities.
- *Artificial placenta*: Design of robust low flow-resistance and high flux oxygenators needs to be optimised with the help of biomimetic models.

Biomimetic *in vitro* and *in silico* models of the placental microcirculations

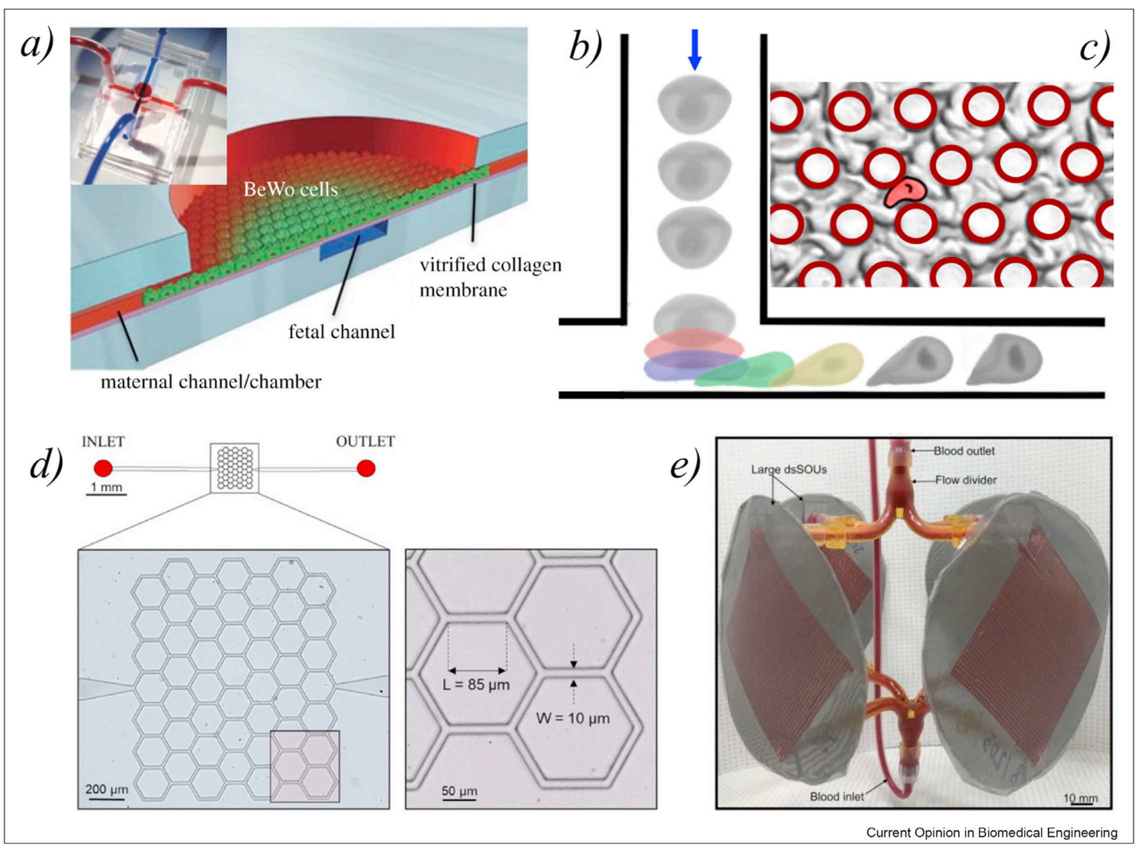
Placental haemodynamics shares important features with circulation in other microvascular networks [25]. Because placental capillaries and pores are of similar size to individual RBCs, cell-scale blood flow needs to be resolved for a haemodynamical model to account for microcirculatory phenomena, such as geometry-induced haematocrit bias and oxygenation heterogeneity [26]. Placental haemodynamics is akin to a suspension flow in a porous medium (i.e., the flow of a heterogeneous mixture of RBCs and other blood constituents), an emerging research topic with many open fundamental questions. On the other hand, there is growing interest in biomimetic micro-engineered 'placenta-on-a-chip' systems that could provide more accurate placental drug transport and toxicology models [16] (Figure 3a). However, there is a paucity of *in vitro* and *in silico* studies of cellular blood flow in placenta-specific geometries [4,14].

Experimental microfluidics of suspension flow in complex geometries

Multiple research fields can inform micro-scale blood flow in the human placenta. Other microvascular systems, such as lung capillary networks [29], share common micro-haemodynamical phenomena [25,30]. Microfluidic sorting devices [32] use complex geometries to direct the flow of cells and particles. Two-phase flows in porous media in the oil-recovery context, while often relating to imbibition/drainage problems, also include emulsion flows [33]. Pore-scale models motivated by subsurface flow problems address the influence of pore-scale geometry on macro-scale flow parameters [34].

There are two experimental avenues for the exploration of haemodynamics in complex geometries like the placenta. Firstly, whole blood or diluted RBC suspensions can be transported through biomimetic porous-medium-like [29] or capillary-network-based

Figure 3



Biomimetic experimental microfluidics and its applications. (**a**) A 'placenta-on-a-chip' micro-engineered device for placental transfer analysis (reproduced from Ref. [27], CC BY 4.0). (**b**) Time-lapse image of an alginate capsule deforming at a T-junction (reproduced from Ref. [28], with the permission of Cambridge University Press). (**c**) A microfluidic model of blood flow in a regular porous medium, with one labelled deformed RBC (red) and marked posts (red circles; adapted from Ref. [29], with the permission of AIP publishing). (**d**) A microfluidic model of blood flow in a biomimetic capillary network (reproduced from Ref. [30], with the permission of AIP publishing). (**e**) Prototype neonatal life-support 'artificial placenta' device (reproduced from Ref. [31], with the permission of AIP publishing). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

[30] artificial structures, thus enabling measurements under well-controlled flow conditions (Figure 3c,d). These measurements have the advantage of retaining biological features related to RBC variability and interaction, but flow conditions need to be carefully monitored to keep the RBCs in a physiological state. Secondly, control over particle properties in addition to flow conditions requires RBC analogues. This approach can reveal the underlying physics of the suspension flow but largely bypasses biological effects. The main challenge is to create physical objects which have biomimetic properties that closely reproduce the mechanics of RBCs in suspension. Potential candidates are elastic beads [35], droplets, vesicles and capsules [36]. While elastic beads offer limited deformability under laboratory flow conditions, droplets and vesicles can exhibit large deformations, but they lack the RBCs' shear elasticity. Liquid droplets encapsulated by an elastic membrane offer the closest analogue to RBCs, but properties like membrane thickness, material properties and inflation need to be finely tuned to access the deformations observed in RBCs (Figure 3b).

The micro-fabrication of complex porous media presents additional challenges. In microfluidics, polydimethylsiloxane (PDMS) is widely used for moulding complex geometries from negatives created by photolithography or micro-milling [37]. These techniques can produce versatile planar and layered geometries but are less suitable for 3D placental geometries. Future prospects of rapid prototyping of 3D architectures are provided by advances in 3D printing technology [38].

Computational models of micro-haemodynamics

Cell-resolved computational models of microscopic blood flow in sparse and complex geometries [2,39,40] have recently provided access to high-resolution flow features (e.g., local shear stresses and pressure gradients in microvasculature), which are very difficult to measure reliably in conventional experiments. These computational models are readily translatable to human placental micro-haemodynamics. Such models rely on efficient spatial and temporal decomposition of complex domains into subsystems for parallel computing and have achieved physiological haematocrit levels (40–60% [39,40]) in large-scale microvasculature, capturing key RBC features, such as cell deformation and dynamics.

Nevertheless, the uncertainty in prescribing inflow/outflow boundary conditions in micro-haemodynamical models (see Section B) requires additional steps, such as network-scale simulations with simplified blood rheology, to provide input data [2,23] (Figure 2c). For cell-scale models to faithfully reproduce physiological transport processes in the human placenta, multi-scale biophysical and biochemical processes (including blood coagulation, cell–cell and cell–surface interactions) need to be incorporated without compromising computational efficiency. Also, longer simulations and larger computational domains are needed to match the realistic temporal and spatial scales over which biological processes occur [39].

Consideration of interfacial features

Thus far, key interfacial micro-/nano-structures at the maternal–fetal interface have been mostly neglected in *in vitro* or *in silico* models. These include the microvilli on the materno-placental trophoblast syncytium layer [24] and the glycocalyx on the endothelium of fetal capillaries [25]. The influence of glycocalyx on the flow of RBCs [41] and the transport of substances across the placental endothelium and trophoblast syncytium remains poorly understood [16]. Recent progress in growing 3D 'organoids' from placental trophoblast cells *in vitro* [42] opens further opportunities for characterising the maternal–fetal interface. With the increasing availability of high-resolution imaging, e.g., transmission electron microscopy, for the placenta [24], a future challenge is to incorporate these interfacial features into blood flow models. This goal may be achieved experimentally by coating channels with cultured trophoblast cells [27], endothelial cells [43] or polymer brushes [44]. However, the disparity in scales, ranging from nanometres for glycoproteins to micrometres for RBCs, hinders the physiologically realistic representation of these features in numerical models.

Scaling up models and simulations

Owing to strong spatial heterogeneity arising from both topological and micro-haemodynamical variations, any microscopic model is likely to be computationally prohibitive at the placental tissue scale. Tractable testing of physiologically relevant hypotheses could be enabled through a combination of optimised computational strategies and mathematical model-reduction approaches.

Code accessibility and scalability

Large-scale parallel simulators of cellular haemodynamics in complex and sparse geometries are primarily based on flow solvers using the lattice-Boltzmann method [2,40] or dissipative particle dynamics [39,45]. Several computational models are available as open-source research software, such as HemeLB [2] and Mirheo [45], which demonstrate excellent scalability and can run on hundreds to thousands of distributed computational (CPU) nodes. Optimisation of the load balancing of computational nodes improves code scalability in simulations of heterogeneous microvascular networks [46]. Nevertheless, the computational efficiency of conventional spatial decomposition schemes is limited by the CPU node communication rate, and efforts have been focused on developing a hybrid parallelism that combines temporal decomposition (computed via GPU) with spatial decomposition [39].

However, even optimised microscopic flow and transport simulators require extensive model parametrisation, uncertainty quantification and validation against tissue- and organ-scale observations, which are not feasible without systematic model-reduction approaches.

Reduced-order modelling and upscaling

A possible solution to harnessing the computational complexity of placental micro-haemodynamics is to implement reduced-order modelling or upscaling techniques. A classic example in which experimental data have been used to inform a reduced-order model is the work of A. R. Pries and T. W. Secomb, who established a set of empirical laws for haematocrit transport through capillary networks [25]. This work is widely used but may not be applicable to maternal flow in the IVS. Upscaling techniques for continuum models over microstructured tissues have been used extensively to investigate tissue properties, often drawing on theoretical developments driven by geophysical applications. These techniques (reviewed by Ref. [47]) largely hinge upon identifying a *representative volume element* (RVE). In a popular method of upscaling, asymptotic homogenisation, RVEs are often assumed to be organised in a periodic array. For a highly heterogeneous and disordered tissue of the human placenta, the assumption of periodicity does not apply, and identifying the features of an RVE is an open and contentious question. Furthermore, spatial scale separation is typically less strong in biological tissues (tens of microns to millimetres) compared to geophysical subsurface applications (nanometres to kilometres). This ultimately restricts the applicability of many approximation methods, meaning new approaches, such as stochastic homogenisation [48] or generalised multiscale finite element methods [49], must be used to construct upscaled models of the placental flow and transport.

Alternatively, network models are commonly employed to investigate the effects of spatial disorder on flow and transport in complex media [34]. Spectral graph theory (which decomposes complex networks according to their topology and physical properties) has shown promise for effective model-reduction and characterisation of heterogeneity in lung airways [50], an approach that could be adapted for the human placenta. However, any possible network model for the placenta will be fundamentally different to those already constructed for other organs (such as brain or tumour vasculature [22,23]) due to differences in network topology. Specifically, developing a coupled model for two distinct placental circulations, the maternal pore network and the fetal vascular network, remains an open challenge. More work is also needed to understand fundamental mechanisms for suspension flows in disordered geometries, such as non-local transport effects [49] and haematocrit heterogeneity [23], in order to inform the development of tissue- and organ-scale models.

Emerging diagnostics and therapies for precision obstetrics medicine

Advances in multiscale *ex vivo* imaging, *in vitro* and *in silico* biomimetic micro-haemodynamical modelling enable more mechanistic understanding and interpretation of clinical imaging (such as Doppler sonography and MRI). Likewise, ‘reverse engineering’ the fundamental building blocks of the human placental microcirculation can help devise new therapeutic strategies in pregnancy complications and optimise the design of adequate biomimetic replicas for clinical applications.

In vivo imaging and management of placental haemodynamics

Doppler ultrasound has been used in maternity care for more than three decades following the recognition that the umbilical artery Doppler waveform is different in pregnancies affected by placental dysfunction [14]. Until recently, all assessments have been made on the basis of the relative peak of velocity compared to diastolic velocity to create either a *pulsatility index* or *resistance index* with gestationally dependent reference ranges created from low-risk pregnancies. Intra-placental Doppler may also have a role in delineating normal placentas from those with dysfunction [14], but existing resolution constraints potentially limit the applicability of this technique in the clinical assessment of placental micro-rheology. Furthermore, the impact of local haematocrit fluctuations in a highly irregular placental IVS, spiral uterine and helical umbilical arteries on the Doppler signal remains to be quantified. There has also been a growing recognition that improving the understanding of why and how Doppler waveforms change will lead to improved risk stratification and more individualised clinical care [14,51].

Placental magnetic resonance imaging (MRI) offers the potential to expand *in vivo* imaging of the placenta beyond what Doppler ultrasound can offer by providing information on flow at a microstructural level [9] and oxygenation status, using functional MRI (e.g., blood-oxygenation-level-dependent (BOLD) T_2* imaging sequence) [52]. However, the spatial resolution of these modalities, which is generally in the millimetric range [18], is still a limiting factor. Structural MRI T_1 and T_2 maps have shown some promise in the early diagnosis of placental dysfunction, but the relationship of data obtained to the placental micro-haemodynamics and postnatal histopathological findings has yet to be fully determined.

Little is known about placental micro-haemodynamics in early pregnancy. For example, one important open question is the interaction of blood flow with porous trophoblast plugs in the spiral arteries that limit the maternal placental circulation until the second trimester, and whose abnormal dynamics are associated with pre-eclampsia and other pathologies [14]. Likewise, placenta-associated bleeding and abruption are challenging to diagnose and characterise pathophysiologically [53].

Better understanding of how micro-haemodynamics and biochemistry interact with complex utero-placental geometries will also inform future therapies and facilitate precision-medicine interventions. In particular, the early establishment of normal and abnormal placental circulation in pregnancy (aided by upscaled biomimetic *in silico* and microfluidic models) could enable differential therapies to be administered to reduce the severity of FGR and associated pregnancy pathologies [3].

Artificial placentas for neonatal support

With the number of pre-term births increasing, considerable attention has been paid to develop critical life-support technology for neonates. In the event of a pre-term birth, the lungs are only partially developed and cannot meet oxygenation needs provided by the placenta *in utero*, often leading to respiratory insufficiency and other conditions that increase neonatal morbidity and mortality.

Several technologies have been developed that aim to mimic the support received by the fetus inside the mother's body, either fully or partially. One class of technology, termed as *artificial womb*, aims to replicate the oxygenation, thermal-control and nutrient-supply functions of the human placenta [54]. An artificial womb is important for pre-term neonates bordering on viability who require a stable extra-uterine environment. Pre-term lamb fetuses (105–130 days gestational age, GA) were maintained in a biobag consisting of artificial amniotic fluid and catheters that connected the fetus to an external pumpless oxygenator, nutrient supply and waste removal device through the umbilical vessels. The device was able to sustain the fetuses physiologically for up to four weeks. Even smaller pre-term lambs (GA 95 days) were sustained for up to five days and shown to have a stable and normal stage of development [55].

The other class of technology known as *artificial placenta* is for more mature pre-term neonates, where respiratory distress is common. In this scenario, oxygenation support in a biomimetic fashion is desired in order to avoid the complications associated with mechanical ventilation. Artificial placental devices consisting of hollow-fiber membrane oxygenators have maintained pre-term lambs (GA 118 days) through a venous–venous connection for over ten days, which enabled the lungs to develop in a normal manner and protected them from injuries associated with ventilation support. Here, a pump is often used to extract the blood and perfuse the oxygenator. In order to extend this technology to smaller neonates, with smaller size and blood volume, alternative microfluidic designs have been considered [31,56] (Figure 3e). The advantage of a microfluidic device is that it can be precisely designed to operate not only in a pumpless manner but also to avoid stagnation zones and high-shear regions, where thrombotic reactions can occur. Very small channel dimensions similar to blood capillaries in the lungs or the placenta, as well as extremely thin gas perfusion membranes, are possible in the microfluidic format. Recently, this format has rescued piglets of the size and blood volume of human neonates from respiratory distress [57], consistently increasing oxygen saturation in the animal from 50–60% to above 80%. This proof of concept in animal models, combined with recent progress in biomimetic *in vitro* and *in silico* models, shows promise for the translation of artificial placenta technology into human trials and for eventual approval and use in human pre-term neonates.

Concluding remarks

Modelling of flow and transport in the human placenta shares some common challenges with other complex biological systems, which include robust extraction and characterisation of the microstructure and identifying appropriate boundary conditions. However, the intertwining of the porous IVS with the irregular feto-placental villous capillary network distinguishes the human placenta not only from other exchange organs but also from the placentas of other non-primate species.

Future progress in the field is expected by a combination of well-controlled biomimetic microfluidics, hybrid and highly parallelised computational micro-haemodynamics and systematic upscaling of these high-resolution models to the organ or device scale.

In addition to the important biomedical and clinical applications in fetal and neonatal medicine, a deeper understanding of suspension flows in complex geometries will address many fundamental questions and stimulate development in other areas of science and engineering.

Author contributions

QZ, ED, KS & QC prepared visualisations; ILC prepared a list of challenges; QZ, ES, TK & ILC contributed to the first draft of Section A (placental physiology); QZ, ED, MOB, TK & ILC contributed to the first draft of Section B (geometry assimilation); QZ, KS, QC, AJ & TK contributed to the first draft of Section C (microfluidics); QZ, ED, OEJ, TK & ILC contributed to the first draft of Section D (upscaling); EDJ, PRS & ILC contributed to the first draft of Section E (clinical applications); QZ, AJ, OEJ, TK & ILC edited the manuscript, and ILC was responsible for overall coordination. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was partially supported by UKRI EPSRC (EP/T008725/1, EP/T008806/1) research grants. QC also acknowledges support by China Scholarship Council (grant No. 202006220020), and MOB acknowledges grants from the Engineering and Physical Sciences Research Council (EPSRC; EP/R029598/1) and Fondation Leducq (17 CVD 03).

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. * Tun WM, Poologasundarampillai G, Bischof H, Nye G, King ONF, Basham M, Tokudome Y, Lewis RM, Johnstone ED, Brownbill P, Darrow M, Chernyavsky IL: **A massively multi-scale approach to characterizing tissue architecture by synchrotron micro-CT applied to the human placenta**. *J R Soc Interface* 2021, **18**: 20210140.
The authors develop a protocol that enables morphological and functional analyses of both maternal and fetal placental domains, using a single high-resolution imaging modality.

2. * Zhou Q, Perovic T, Fechner I, Edgar LT, Hoskins PR, Gerhardt H, Krüger T, Bernabeu MO: **Association between erythrocyte dynamics and vessel remodelling in developmental vascular networks**. *J R Soc Interface* 2021, **18**:20210113.
This study simulates RBCs dynamics in realistic microvasculature and shows the important role of cellular flow in the remodelling of vascular networks. The developed image-based computational framework can be translated to other microvascular systems.

3. Burton GJ, Jauniaux E: **Pathophysiology of placental-derived fetal growth restriction**. *Am J Obstet Gynecol* 2018, **218**:S745–S761.

4. Jensen OE, Chernyavsky IL: **Blood flow and transport in the human placenta**. *Annu Rev Fluid Mech* 2019, **51**:25–47.

5. Erlich A, Pearce P, Mayo RP, Jensen OE, Chernyavsky IL: **Physical and geometric determinants of transport in feto-placental microvascular networks**. *Sci Adv* 2019, **5**, eaav6326.

6. Sun C, Groom KM, Oyston C, Chamley LW, Clark AR, James JL: **The placenta in fetal growth restriction: what is going wrong?** *Placenta* 2020, **96**:10–18.

7. Carrasco-Wong I, Moller A, Giachini FR, Lima VV, Toledo F, Stojanova J, Sobrevia L, Martín SS: **Placental structure in gestational diabetes mellitus**. *Biochim Biophys Acta (BBA) - Mol Basis Dis* 2020, **1866**:165535.

8. ** de Freitas MAR, da Costa AV, Medeiros LA, Cunha LM, Filho UC, da Silva Garrote Filho M, Diniz ALD, Penha-Silva N: **The role of the erythrocyte in the outcome of pregnancy with pre-eclampsia**. *PLoS One* 2019, **14**, e0212763.
The authors identify gene expressions associated with RBC biomechanics and explore the role of RBC properties in the pathophysiology of pre-eclampsia.

9. * Dellschaft NS, Hutchinson G, Shah S, Jones NW, Bradley C, Leach L, Platt C, Bowtell R, Gowland PA: **The haemodynamics of the human placenta *in utero***. *PLoS Biol* 2020, **18**, e3000676.
This work makes the first measurements of the velocity of bulk movement through the placenta using phase contrast angiography MRI, indicating slow flow in the IVS and hitherto unappreciated rapid utero-placental venous drainage.

10. Brook A, Hoaksey A, Gurung R, Yoong EEC, Sneyd R, Baynes GC, Bischof H, Jones S, Higgins LE, Jones C, Greenwood SL, Jones RL, Gram M, Lang I, Desoye G, Myers J, Schneider H, Hansson SR, Crocker IP, Brownbill P: **Cell free hemoglobin in the fetoplacental circulation: a novel cause of fetal growth restriction?** *Faseb J* 2018, **32**:5436–5446.

11. Seo J, Conegliano D, Farrell M, Cho M, Ding X, Seykora T, Qing D, Mangalmurti NS, Huh D: **A microengineered model of RBC transfusion-induced pulmonary vascular injury**. *Sci Rep* 2017, **7**:3413.

12. Roberts H, Bourque SL, Renaud SJ: **Maternal iron homeostasis: effect on placental development and function**. *Reproduction* 2020, **160**:R65–R78.

13. Baptista LC, Costa ML, Surita FG, Rocha CdS, Lopes-Cendes I, de Souza BB, Costa FF, de Melo MB: **Placental transcriptome profile of women with sickle cell disease reveals differentially expressed genes involved in migration, trophoblast differentiation and inflammation**. *Blood Cells Mol Dis* 2020, **84**:102458.

14. Clark AR, Lee TC, James JL: **Computational modeling of the interactions between the maternal and fetal circulations in human pregnancy**. *WIREs Mech Dis* 2021, **13**, e1502.

15. Lewis RM, Cleal JK, Sengers BG: **Placental perfusion and mathematical modelling**. *Placenta* 2020, **93**:43–48.

16. Pemathilaka RL, Reynolds DE, Hashemi NN: **Drug transport across the human placenta: review of placenta-on-a-chip and previous approaches**. *Interface Focus* 2019, **9**:20190031.

17. Tongpob Y, Wyrwoll C: **Advances in imaging feto-placental vasculature: new tools to elucidate the early life origins of health and disease**. *J Dev Orig Health Dis* 2021, **12**:168–178.

18. Srinivasan V, Melbourne A, Oyston C, James JL, Clark AR: **Multiscale and multimodal imaging of utero-placental anatomy and function in pregnancy**. *Placenta* 2021, **112**:111–122.

19. ** Pietsch M, Ho A, Bardanzellu A, Zeidan AMA, Chappell LC, Hajnal JV, Rutherford M, Hutter J: **APPLAUSE: automatic prediction of placental health via U-net segmentation and statistical evaluation**. *Med Image Anal* 2021, **72**:102145.
The authors develop a machine learning pipeline for automated segmentation of placental MRI scans and prediction of placental insufficiency between 27 and 33 weeks.

20. * Torquato S: **Predicting transport characteristics of hyperuniform porous media via rigorous microstructure-property relations**. *Adv Water Resour* 2020, **140**:103565.
The study revisits geometric and physics-based approaches to the transport in disordered porous media, showing the intricate role of microstructural correlations and pore-size distributions.

21. * Stolz BJ, Kaeppler J, Markelc B, Mech F, Lipsmeier F, Muschel RJ, Byrne HM, Harrington HA: **Multiscale topology characterises dynamic tumour vascular networks**. *Sci Adv* 2020. In Press, https://ora.ox.ac.uk/objects/uuid:291cd01d-2df2-4f96-875a-37da28617a63.
The study applies topological data analysis to complex tumour vascular networks, capturing inherent multi-scale organisation and vessel connectivity. The developed approach offers great potential for relating the form and function in other complex microvascular networks.

22. * Sweeney PW, d'Esposito A, Walker-Samuel S, Shipley RJ: **Modelling the transport of fluid through heterogeneous, whole tumours *in silico***. *PLoS Comput Biol* 2019, **15**, e1006751.
This work develops an integrated computational framework for large-scale modelling of blood flow and interstitial fluid transport in vascular tumours, which is informed by *ex vivo* and *in vivo* experiments.

23. * Schmid F, Tsai PS, Kleinfeld D, Jenny P, Weber B: **Depth-dependent flow and pressure characteristics in cortical microvascular networks**. *PLoS Comput Biol* 2017, **13**, e1005392.
This work simulates RBC dynamics in a realistic cerebral mouse vasculature, showing the impact of haematocrit heterogeneities on flow distribution in the network.

24. Lewis RM, Pearson-Farr JE: **Multiscale three-dimensional imaging of the placenta**. *Placenta* 2020, **102**:55–60.

25. Secomb TW: **Blood flow in the microcirculation**. *Annu Rev Fluid Mech* 2017, **49**:443–461.

26. Bernabeu MO, Köry J, Grogan JA, Markelc B, Beardo A, d'Avezac M, Enjalbert R, Kaeppler J, Daly N, Hetherington J, Krüger T, Maini PK, Pitt-Francis JM, Muschel RJ, Alarcón T, Byrne HM: **Abnormal morphology biases hematocrit**

distribution in tumor vasculature and contributes to heterogeneity in tissue oxygenation. *Proc Natl Acad Sci Unit States Am* 2020, **117**:27811–27819.

27. Miura S, Sato K, Kato-Negishi M, Teshima T, Takeuchi S: **Fluid shear triggers microvilli formation via mechanosensitive activation of TRPV6**. *Nat Commun* 2015, **6**:8871.

28. Häner E, Heil M, Juel A: **Deformation and sorting of capsules in a T-junction**. *J Fluid Mech* 2019, **885**.

29. ** Stauber H, Waisman D, Korin N, Sznitman J: **Red blood cell dynamics in biomimetic microfluidic networks of pulmonary alveolar capillaries**. *Biomicrofluidics* 2017, **11**, 014103.
The authors investigated RBC suspension flows in biomimetic artificial structures, representing lung capillary networks, enabling haemodynamical measurements under well-controlled flow conditions.

30. * Mantegazza A, Clavica F, Obrist D: ***In vitro* investigations of red blood cell phase separation in a complex microchannel network**. *Biomicrofluidics* 2020, **14**, 014101.
This experimental study comprehensively characterises RBC flux partitioning in complex networks and highlights the importance of both local and non-local effects on the haematocrit distribution.

31. Dabaghi M, Fusch G, Saraei N, Rochow N, Brash JL, Fusch C, Ravi Selvaganapathy P: **An artificial placenta type microfluidic blood oxygenator with double-sided gas transfer microchannels and its integration as a neonatal lung assist device**. *Biomicrofluidics* 2018, **12**, 044101.

32. Catarino SO, Rodrigues RO, Pinho D, Miranda JM, Minas G, Lima R: **Blood cells separation and sorting techniques of passive microfluidic devices: from fabrication to applications**. *Micromachines* 2019, **10**:593.

33. Perazzo A, Tomaiuolo G, Preziosi V, Guido S: **Emulsions in porous media: from single droplet behavior to applications for oil recovery**. *Adv Colloid Interface Sci* 2018, **256**:305–325.

34. ** Alim K, Parsa S, Weitz DA, Brenner MP: **Local pore size correlations determine flow distributions in porous media**. *Phys Rev Lett* 2017, **119**:144501.
This study compares numerical, analytical and experimental models of flow through two-dimensional disordered porous media, concluding that even weak microstructutal disorder significantly impacts flow distribution.

35. Pinho D, Carvalho V, Gonçalves IM, Teixeira S, Lima R: **Visualization and measurements of blood cells flowing in microfluidic systems and blood rheology: a personalized medicine perspective**. *J Personalized Med* 2020, **10**:249.

36. Barthès-Biesel D: **Motion and deformation of elastic capsules and vesicles in flow**. *Annu Rev Fluid Mech* 2016, **48**:25–52.

37. Niculescu AG, Chircov C, Bîrcă AC, Grumezescu AM: **Fabrication and applications of microfluidic devices: a review**. *Int J Mol Sci* 2021, **22**:2011.

38. Nielsen AV, Beauchamp MJ, Nordin GP, Woolley AT: **3D printed microfluidics**. *Annu Rev Anal Chem* 2020, **13**:45–65.

39. ** Blumers AL, Yin M, Nakajima H, Hasegawa Y, Li Z, Karniadakis GE: **Multiscale parareal algorithm for long-time mesoscopic simulations of microvascular blood flow in zebrafish**. *Comput Mech* 2021, **68**:1131–1152.
The study applies a multiscale parallel-in-time algorithm to simulate transient blood flow in realistic vasculature, enabling computations over physiological time scales.

40. * Ames J, Puleri DF, Balogh P, Gounley J, Draeger EW, Randles A: **Multi-GPU immersed boundary method hemodynamics simulations**. *J Comput Sci* 2020, **44**:101153.
This study simulates dense cellular blood flow, resolving millions of discrete RBCs through distributed GPU-acceleration and thus enabling computational micro-haemodynamics in large-scale physiological systems.

41. Jiang XZ, Goligorsky MS, Luo KH: **Cross talk between endothelial and red blood cell glycocalyces via near-field flow**. *Biophys J* 2021, **120**:3180–3191.

42. Cherubini M, Erickson S, Haase K: **Modelling the human placental interface in vitro – a review**. *Micromachines* 2021, **12**:884.

43. Tsvirkun D, Grichine A, Duperray A, Misbah C, Bureau L: **Microvasculature on a chip: study of the endothelial surface layer and the flow structure of red blood cells**. *Sci Rep* 2017, **7**:45036.

44. Bureau L, Coupier G, Dubois F, Duperray A, Farutin A, Minetti C, Misbah C, Podgorski T, Tsvirkun D, Vysokikh M: **Blood flow and microgravity**. *Compt Rendus Mec* 2017, **345**:78–85.

45. Alexeev D, Amoudruz L, Litvinov S, Koumoutsakos P: **Mirheo: high-performance mesoscale simulations for microfluidics**. *Comput Phys Commun* 2020, **254**:107298.

46. Kotsalos C, Latt J, Beny J, Chopard B: **Digital blood in massively parallel CPU/GPU systems for the study of platelet transport**. *Interface Focus* 2021, **11**:20190116.

47. Battiato I, Ferrero VPT, O' Malley D, Miller CT, Takhar PS, Valdés-Parada FJ, Wood BD: **Theory and applications of macroscale models in porous media**. *Transport Porous Media* 2019, **130**:5–76.

48. Russell MJ, Jensen OE: **Homogenization approximations for unidirectional transport past randomly distributed sinks**. *IMA J Appl Math* 2020, **85**:161–189.

49. Chung ET, Efendiev Y, Leung WT, Vasilyeva M, Wang Y: **Non-local multi-continua upscaling for flows in heterogeneous fractured media**. *J Comput Phys* 2018, **372**:22–34.

50. Whitfield CA, Latimer P, Horsley A, Wild JM, Collier GJ, Jensen OE: **Spectral graph theory efficiently characterizes ventilation heterogeneity in lung airway networks**. *J R Soc Interface* 2020, **17**:20200253.

51. ** Cahill LS, Stortz G, Ravi Chandran A, Milligan N, Shinar S, Whitehead CL, Hobson SR, Ayyathurai V, Rahman A, Saghian R, Jobst KJ, McShane C, Block-Abraham D, Seravalli V, Laurie M, Millard S, Delp C, Wolfson D, Baschat AA, Murphy KE, Serghides L, Morgen E, Macgowan CK, Parks W, Kingdom JC, Sled JG: **Wave reflections in the umbilical artery measured by Doppler ultrasound as a novel predictor of placental pathology**. *EBioMedicine* 2021, **67**:103326.
The study demonstrated the feasibility of probing the mechanical status of feto-placental vasculature *in vivo* via a reflected pressure wave component in Doppler sonography.

52. Ingram E, Morris D, Naish J, Myers J, Johnstone E: **MR imaging measurements of altered placental oxygenation in pregnancies complicated by fetal growth restriction**. *Radiology* 2017, **285**:953–960.

53. Fadl SA, Linnau KF, Dighe MK: **Placental abruption and hemorrhage – review of imaging appearance**. *Emerg Radiol* 2019, **26**:87–97.

54. ** Partridge EA, Davey MG, Hornick MA, McGovern PE, Mejaddam AY, Vrecenak JD, Mesas-Burgos C, Olive A, Caskey RC, Weiland TR, Han J, Schupper AJ, Connelly JT, Dysart KC, Rychik J, Hedrick HL, Peranteau WH, Flake AW: **An extra-uterine system to physiologically support the extreme premature lamb**. *Nat Commun* 2017, **8**:15112.
In this pioneering study, the authors were able to sustain extremely premature lamb fetuses physiologically for up to four weeks.

55. Usuda H, Watanabe S, Saito M, Sato S, Musk GC, Fee ME, Carter S, Kumagai Y, Takahashi T, Kawamura MS, Hanita T, Kure S, Yaegashi N, Newnham JP, Kemp MW: **Successful use of an artificial placenta to support extremely preterm ovine fetuses at the border of viability**. *Am J Obstet Gynecol* 2019, **221**:69.e1–69.e17.

56. Thompson AJ, Ma LJ, Plegue TJ, Potkay JA: **Design analysis and optimization of a single-layer PDMS microfluidic artificial lung**. *IEEE Trans Biomed Eng* 2019, **66**:1082–1093.

57. * Dabaghi M, Rochow N, Saraei N, Fusch G, Monkman S, Da K, Shahin-Shamsabadi A, Brash JL, Predescu D, Delaney K, Fusch C, Selvaganapathy PR: **A pumpless microfluidic neonatal lung assist device for support of preterm neonates in respiratory distress**. *Adv Sci* 2020, **7**:2001860.
In this study, a pumpless microfluidic oxygenator rescued piglets, of the size and blood volume of human neonates, from the respiratory distress.