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The Physical Placenta

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Subhead: Physical processes such as flow and solute transport link the human placenta's intricate structure to its role as a fetal life-support system.

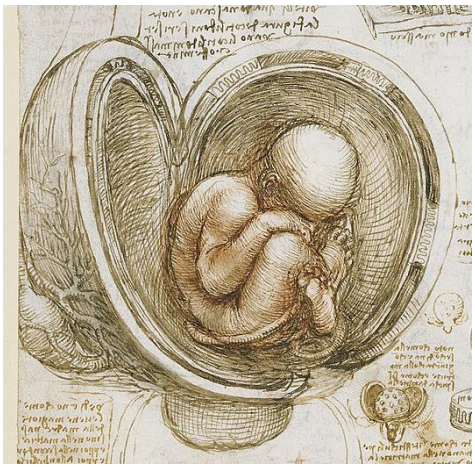
The placenta is unique in being a short-lived but highly versatile organ, providing critical life support to the developing fetus during pregnancy. Modern imaging techniques reveal its complex microstructure, which is intimately connected to the placenta's primary role in exchanging solutes between mother and fetus. Computational image-based modeling helps us understand how the intricate spatial organization of maternal and fetal blood vessels influences solute exchange, and how placental function might be disrupted in disease. Here, we provide a whistle-stop tour of the organ and of physics-based approaches to understanding its remarkable life-sustaining role.

Structure and function

Before you were born, you were nourished by a unique and extraordinary organ: the placenta. Your placenta (the placenta is a fetal organ) formed an interface between the nutrient-rich blood in your mother's circulation, and your circulation, without the two blood supplies ever mixing. This provided a life-support system that effectively served as your lungs, gut, kidney and liver and supported healthy growth.

Although many anatomists have investigated pregnancy and the placenta, including Leonardo Da Vinci (Box 1), William Harvey and Nicolaas Hoboken (Fig. 1), historically the belief was that the blood circulations of mother and child had a direct connection. The confirmation that there was functional separation of the two circulations is often credited to the Scottish anatomist and obstetrician William Hunter in the 1770s. Since then, our understanding of the anatomy and function of the placenta has evolved significantly, thanks to a recent explosion of imaging techniques that have provided detailed insights into its structure.

Da Vinci is renowned for his detailed anatomical drawings, and his depiction (below) of the fetus and uterus is no exception. In his descriptions of the placenta, he described the interface between maternal and fetal blood to reflect interwoven hands and suggested a separation between the two circulations. However, the prevailing view of early philosophers and many anatomists, from ancient Greek texts through to the 18th Century, was that there was a direct connection between the maternal arteries of the uterus and the fetus (at the placenta). 17th Century anatomists such as Harvey and Hoboken questioned this view, just as Da Vinci had, but they did not have the tools to confirm the functional separation of the two circulations. This is credited to William Hunter, who described how wax injected into the uterine circulation did not appear in the fetal circulation, and likewise wax injected into the umbilical vessels did not enter the uterus; he presented his findings in his detailed anatomical atlas "The Gravid Uterus." For a comprehensive history of the understanding of the placenta see Ref. 13.



Source: https://commons.wikimedia.org/wiki/File:Leonardo_da_Vinci_-_Studies_of_the_foetus_in_the_womb.jpg

Fig. 1a (a) *The frontispiece of Hoboken's (1669) anatomical text.*[9] *While this depiction of a newborn infant has some curious idiosyncrasies, the placenta is depicted reasonably accurately.* Source: https://iiif.library.utoronto.ca/image/v2/anatomia:RBAI087_0002/full/full/0/default.jpg

Fig. 1b (b) *A more detailed illustration from Hoboken*[9] *showing fetal blood vessels radiating out from the umbilical cord over the upper surface of the placenta, and then entering villous trees beneath.* Source: https://iiif.library.utoronto.ca/image/v2/anatomia:RBAI087_0013/full/full/0/default.jpg

Fetal blood vessels within the placenta occupy complex tree-like structures, called villous trees (Fig. 1b). Despite being packed within a disc the size of a frisbee, the placenta has a huge surface

area for exchange, roughly 10 m^2, or $1/10^{th}$ of the surface area provided by the adult human lungs. A unique multinucleated cell (the syncytiotrophoblast) covers the entire surface of the placenta, providing a barrier between maternal and fetal blood. The fetal blood vessels themselves branch from the umbilical cord, over the fetal-facing (or chorionic) surface of the placenta and into the placental tissue within the villous trees. Millions of placental capillaries sit close to the surface of the placenta, where nutrients and waste are exchanged with maternal blood (Fig. 2).

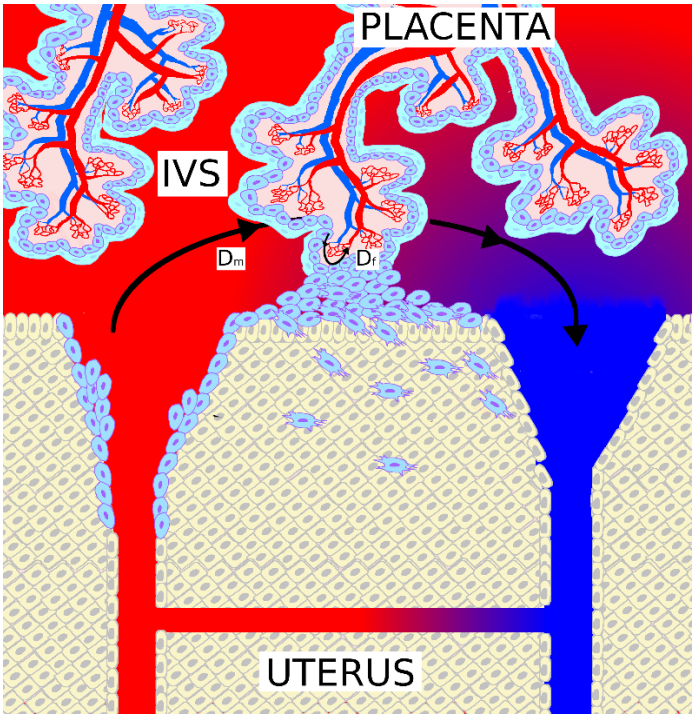


Fig. 2 *Oxygenated maternal blood (red) flows from a spiral artery in the wall of the uterus into the intervillous space (IVS). Here it flows past villous trees before being collected in a nearby decidual vein (blue), having lost its oxygen to fetal blood flowing within capillary networks within the villous trees. The maternal and fetal circulations are separated by the syncytiotrophoblast (cyan) and other placental tissues, including trophoblast cells (light blue) that invade and remodel the wall of the uterus. Fetal and maternal Damköhler numbers D_f and D_m (see "Exchange Physics") characterize solute exchange. Arrows show flow directions of maternal and fetal blood. A shunt vessel is also illustrated, connecting the uterine artery and vein.*

To establish a successful pregnancy, the placental villous trees not only have to develop effectively, but the placenta must also ensure a good blood supply to its surface from the uterus. This process is extraordinary: placental cells invade into the uterine wall and transform the walls of the smallest uterine blood vessels into wide non-muscular channels to allow a significantly increased supply of blood in late pregnancy (estimated to be increased by 15 times compared to the blood supply to the non-pregnant uterus). Even the blood vessels that are not actively

invaded by placental cells increase in size (up to two-fold) and their behavior is modulated by the hormones of pregnancy, which have a placental origin.

The success of a pregnancy therefore relies on establishing two blood supply systems, one fetal (the placenta) and one maternal (the uterus), as well as the development of the fetus itself. The interface between the maternal and fetal circulations is also of critical importance. The two circulations need to be in close contact for effective exchange, but it is dangerous if they mix or if potentially harmful compounds cross over to the fetus. Disruptions to blood flow in either circulation can impact the structure of the placenta and the exchange barrier between maternal and fetal blood.

Understanding pathologies of the placenta relies on a genuine understanding of what is "normal." This varies widely between human pregnancies, and even more so between species. Some pathologies of pregnancy are unique to humans, in part because placentation has evolved to be remarkably different between placental mammals. Accessing the placenta *in vivo* is challenging: we cannot look inside a pregnant mother daily, nor can we use techniques that involve ionizing radiation. However, the placenta is delivered at the end of pregnancy, which allows studies of its structure and function outside of the body.

The inaccessibility of the placenta in an ongoing pregnancy means that there is an important role for physical scientists in determining what makes a healthy placenta. We can readily observe snapshots of anatomical structure in delivered placentas, but we need tools to link these snapshots to the drivers of function and dysfunction in the nine months prior to delivery. Physics-based models help link structure to function, and so help in understanding what to look out for in clinical practice, where routine ultrasound scans provide a low-resolution insight into placental function during pregnancy.

Pathologies

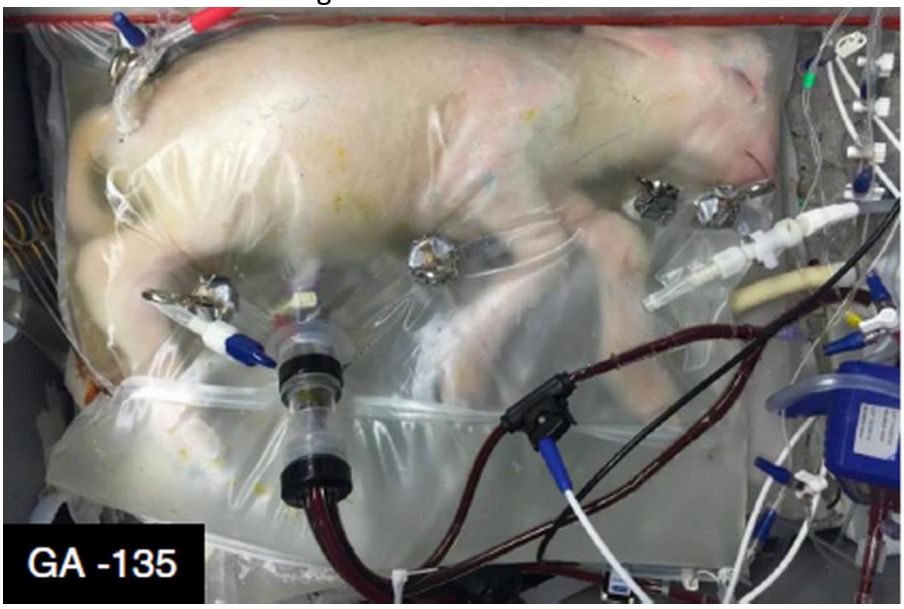
Several pathologies that relate to the placenta have significant impacts on the success of a pregnancy, and potentially life-long effects on the baby born from that pregnancy.[1] The biggest risk for a pregnancy is stillbirth, which has devastating consequences for the families involved. The greatest contributor to stillbirth risk is a condition known as fetal growth restriction (FGR), where a fetus does not grow as well as it should. The condition pre-eclampsia is often associated with a poorly adapted circulation in the uterus and it often accompanies FGR. If untreated (usually by a premature delivery), pre-eclampsia can lead to eclampsia which is critically dangerous to both mother and fetus.

Both FGR and pre-eclampsia are associated with a reduced density of villous structures in the placenta (Fig. 3b, compared with a normal placenta Fig. 3a). Diabetes in pregnancy often leads to opposite effects, with an over-proliferation of blood vessels within the placenta (Fig. 3c). All these pregnancy complications put the child at risk of cardiovascular (and other health

conditions) later in life and are associated with a compromised structure, leading to dysfunction of the fetal placenta or the uterine circulation. This is why many complications can lead to either premature delivery or stillbirth.

Pregnancy complications are notoriously difficult to predict. Problems in low-risk pregnancies can be hard to spot and need to be picked up early to ensure that the pregnancy is monitored effectively. Monitoring reduces stillbirth risk in many cases, as it allows decisions such as when to deliver to be made at the appropriate time. To detect problems early we need a solid physical understanding of what processes lead to a pathological pregnancy – and a way to detect these processes with the clinical tools available. Despite significant progress, replicating the many roles of the placenta remains a significant technological challenge (Box 2).

The mystery of childbirth has always fascinated humanity. Still, from da Vinci's times to the present, our management of pregnancy and its complications has not changed dramatically (except for assisted reproductive technologies, such as *in vitro* fertilization, that already help many families to experience the happiness of parenthood). However, recently, reproductive bioengineering has moved even further than that into supporting pregnancies with premature delivery. For example, a healthy lamb from an extremely premature fetus has been successfully grown for nearly a month outside maternal body in an incubator-like device[14] (illustrated below). Although reproductive technologies remain remote from Huxley's "Brave New World", proof-of-concept artificial wombs suggest that the impacts from premature birth could be mitigated. However, many practical challenges remain, including the design of efficient and robust solute-exchange systems that do not over-burden the delicate fetal or neonatal heart.[18] With deeper understanding of the unique physical aspects of the human placenta, the artificial womb and placenta technologies could help rescue premature babies and ensure their life-long health.



*Source: Partridge et al. (2017) (*doi.org/10.1038/ncomms15112*)*

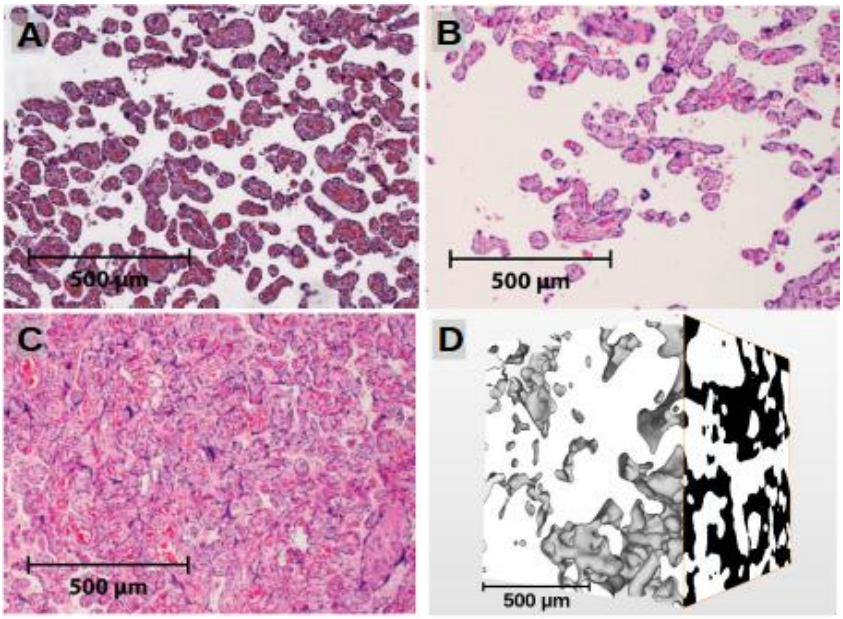


Fig. 3 *(A-C) are cross-sections of placental tissue (from Ref. 15) showing IVS (pale) and villous trees (stained dark), illustrating typical structures for (A) normal, (B) pre-eclamptic and (C) diabetic placentas. (D) Shows a 3D image of placental tissue (white) and the IVS region (dark) obtained by synchrotron X-ray tomography (unpublished, based on Ref. 17).*

Imaging

Characterization of an evolving human placenta requires a variety of complementary imaging techniques.[4,12] Traditional light and electron microscopy and ultrasound imaging have recently been supplemented by magnetic resonance imaging (MRI) and micro-computed tomography (CT).[2,18] Synchrotron X-ray tomography (sCT) of soft biological tissues resolves structures across four orders of magnitude (from microns to centimeters). Application of sCT to the intricate multiscale architecture of the human placenta is opening new windows into placental pathology and providing new opportunities for image-based modelling. Here, recent advances have been enabled not only by robust sample preparation and scanning techniques, but also by efficient semi-automated segmentation based on machine learning algorithms.

However, even with access to detailed placental microstructure, there remains a gap in our understanding of how the physics of flow and transport at the organ scale emerges from the dominant processes at the finest anatomical scales. Furthermore, clinical diagnostic tools, such as MRI and Doppler ultrasound, bring an additional layer of complexity, as interpretation of images relies on the physics of imaging technologies and multiple assumptions about the geometry and physical properties of the probed tissue. Future advances in clinical imaging

depend on a new generation of physics-based models that can assimilate data from diverse sources across multiple length scales.

Probing the heterogenous multiscale structure of the human placenta also poses significant challenges in uncertainty quantification. Many statistical estimates of geometric and material properties of complex soft tissues are intrinsically scale dependent.[18] Care is needed to identify a representative region of interest and to characterize associated fluctuations in key quantities (e.g., specific volumetric and surface area densities, or spatial correlation length scales).

Exchange physics

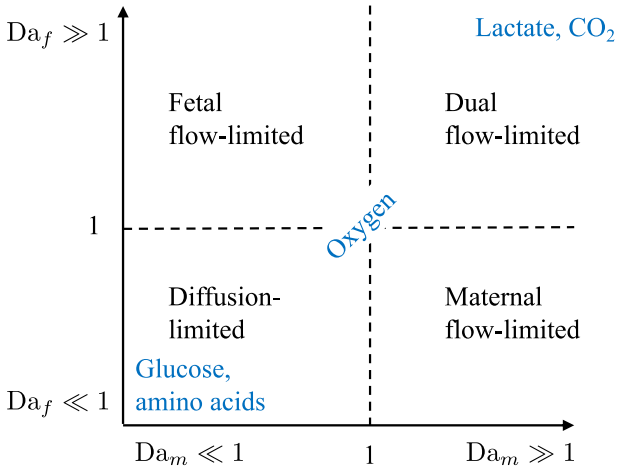


Fig. 4 *Placental exchange regimes for a selection of representative solutes (adapted from Ref. 7). The dimensionless quantities Da_f and Da_m are the fetal and maternal Damköhler numbers respectively. The strength of transport by maternal and fetal blood flow is proportional to $1/Da_m$ and $1/Da_f$ respectively.*

Small molecules (such as oxygen) diffuse readily across the syncytiotrophoblast, which acts as a barrier between maternal and fetal blood (Fig. 2). Larger molecules, if they can cross at all, diffuse more slowly; some (such as amino acids and glucose) require active transport to cross cell membranes, requiring the involvement of specific membrane-bound proteins or intracellular vesicles to reach the fetus.[16]

Suppose that it takes a typical time T_S for a particular solute to cross the syncytiotrophoblast, either by diffusion or active transport. Fetal blood delivered to a terminal villus will spend a typical time T_V (say) passing through its capillary network before being returned to the larger conducting vessels of the fetoplacental circulation. If T_V is sufficiently small compared to T_S, then

diffusive or active transport across the syncytiotrophoblast regulates exchange (it is the "rate-limiting" step in the transport pathway). Exchange in this case is often called "diffusion-limited." If T_S is much smaller than T_V, then the rate at which solute is delivered to the fetus is regulated by how fast the blood flowing within the capillaries can carry solute through the villus. This case is called "flow-limited".[8]

We can characterize the way in which a given solute moves across the walls of a terminal villus using a dimensionless number, the fetal Damköhler number Da_f, defined as the ratio of advective to diffusive fluxes in a typical villus (Fig. 4). Da_f is proportional to the ratio T_V/T_S: very small Da_f corresponds to diffusion-limited transport, and very large Da_f to flow-limited transport. Overall, for fixed maternal conditions, the rate at which solute passes between the IVS and the fetal circulation rises from low values (in the flow-limited state, regulated by the weak fetal flow) to a maximum value in the diffusion-limited state. The maximum solute flux that a villus can absorb in the diffusion-limited state can be expressed as $L_v D_t \Delta C$, where L_v is a length scale that captures the complex geometric structure of the villus, D_t is a diffusion coefficient in fetal tissue and ΔC is the concentration difference between fetal and maternal concentrations. L_v can be interpreted, crudely, as the typical surface area for exchange divided by the typical distance over which solutes must diffuse through villous tissue. L_v is defined by the shape of the villus and the arrangement of capillaries within it.[7]

Suppose that it takes a typical time T_m for a packet of maternal blood to pass through the IVS, from spiral artery to decidual vein. If each villus exchanges solutes with a volume V_m of the IVS, then a characteristic rate at which solute can be exchanged is then $L_v D_t/V_m$ (assuming diffusion-limited transport in the villi). Comparing this to the transit rate $1/T_m$ defines a dimensionless maternal Damköhler number Da_m that is proportional to $T_m L_v D_t/V_m$. Once again, diffusion-limited and flow-limited states are defined by the size of Da_m: very small Da_m corresponds to fast flow and relatively slow solute exchange, regulated by the exchange capacity of the villi, with maternal blood leaving the IVS before villi have had time to exchange all the solute; large Da_m describes the case when maternal blood flows slowly relative to the exchange rate, meaning that solute can be extracted from maternal blood long before it has left the IVS, but with the net flux passing between mother and fetus falling short of the full exchange capacity of the villi.

Solute exchange is therefore regulated by the strength of both maternal and fetal circulations (Fig. 4), being weakest when transport is flow-limited for both maternal and fetal circulations (large Da_f and large Da_m), rising to a plateau where both become diffusion-limited (small Da_f and small Da_m). One might imagine that there is a "sweet spot," with both Da_f and Da_m being of order unity, allowing effective transport without involving excessively rapid flows. However, a striking feature of placental transport is the variability in Damköhler numbers for different solutes: smaller molecules such as CO_2 are more likely to be flow limited, whereas larger molecules such as glucose are likely to be diffusion limited, with both being transported simultaneously.[7] (This simple picture is enriched when accounting for additional biochemical processes,[8,11] such as the binding of oxygen to hemoglobin, and when accounting for metabolism of solutes by placental

tissue itself). The complex architecture of the placenta must accommodate the transport of a broad range of solutes, rather than be optimized for a single purpose. A more appropriate question to ask is how transport of all solutes may be compromised in disease, when both flow and solute exchange are directly influenced by structural factors that influence both the diffusive exchange capacity and the resistance to flow. If villi are packed too densely, as in diabetes (Fig. 3c), villi are abundant but they present a high resistance to flow; if villi are packed too sparsely, as in pre-eclampsia (Fig. 3a), flow resistance is low, but the diffusive exchange capacity of the placenta is significantly reduced.

A multiscale complex system

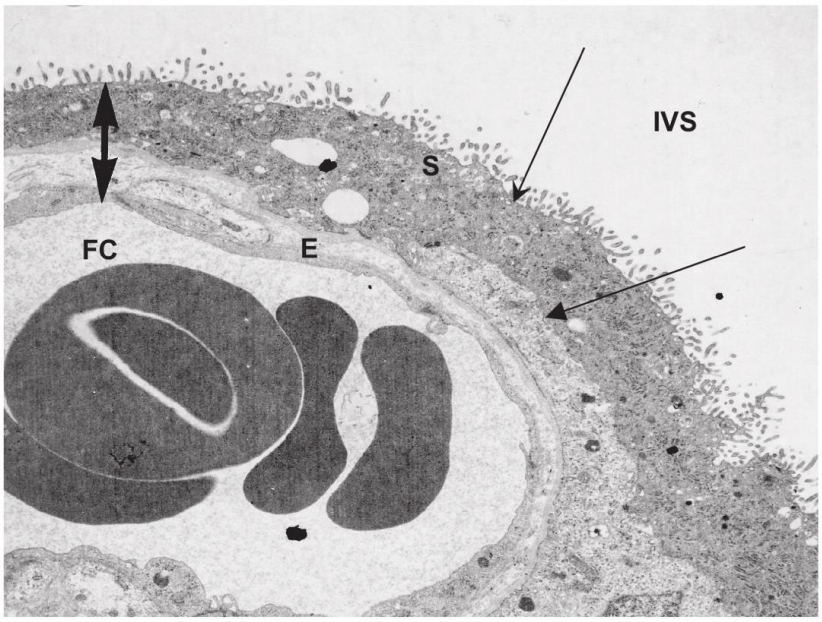


Fig. 5a *The placental exchange barrier, showing intervillous space (IVS), syncytiotrophoblast (S) and a fetal capillary (FC) lined by endothelial cells € and containing red blood cells of maximum diameter of approximately 8 µm. The double-headed arrow illustrates the distance that solutes must travel between maternal and fetal blood (reproduced from Ref. 6).*

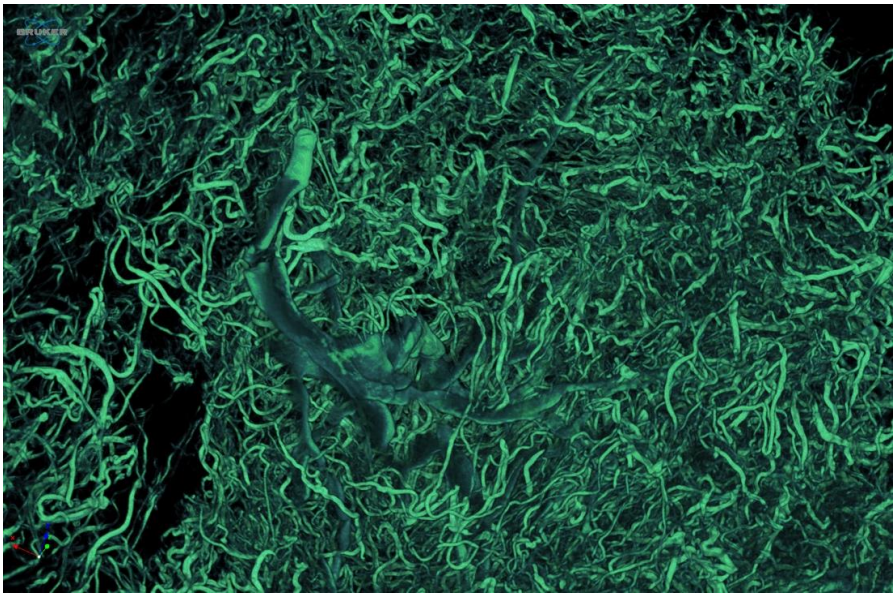


Fig. 5b *A microCT image of the fetoplacental vascular network highlighting the complexity of the vasculature and the transition between large and small placental blood vessels. The largest visible blood vessel has a diameter of 450um; the image resolution is 5μm. Acknowledgements: Vijayalakshmi Srinivasan, Mary Spring, Joanna James (University of Auckland; based on Ref. 11).*

The placenta's function is regulated by its morphology across multiple spatial scales. At the cellular scale, the particulate nature of blood influences its flow properties in fetal capillaries and the smallest pores of the IVS,[18] while the thickness of the syncytiotrophoblast regulates local solute exchange (Fig. 5a). The larger-scale vasculature forms an intricate network of bewildering complexity (Fig. 5b). The number of individual villi in the placenta is estimated to be over 10 million.[1] With at least one artery and vein (and many capillaries) within each villous it is infeasible to represent every blood vessel in assessing the physics of blood flow in the whole placenta. Two tools that simplify blood flow physics in the placenta are homogenization (a smoothing approach used in 'porous medium' models) and image-based simulation of transport in vascular networks that are representative of a particular scale of interest.

Homogenization, to date, has mostly been used to simulate blood flow in the IVS (Fig. 2) which can be considered as a disorganized network of "pores" through which maternal blood percolates around obstacles (villous trees). Flow through a porous medium has been widely studied, particularly in geophysical applications, and modelling techniques have been adapted to the placenta.[11] Early studies used 2D cross-sectional images of placental tissue (such as Fig. 3a) to quantify spatially averaged 'pore spaces' and to predict maternal blood flow through functional regions of the placenta, fed by a single maternal artery. More recently, a trend toward investigating meso-scale pore structures in 3D (such as Fig. 3d) has allowed incorporation of spatially varying tissue properties in these simulations. These models have brought insights into how the observed structure of the placenta at delivery relates to both maternal blood flow and oxygenation.

Regarding fetal and uterine circulations, branching blood vessels have been considered mathematically as graphical networks at multiple scales, from disordered capillary networks to more regularly branching large-scale vascular networks. In these network models, simplified governing equations for blood flow are used. They do not necessarily incorporate flow disturbances at branching points of vessels, nor do they explicitly track the movement of oxygen-carrying red blood cells in these vessels. However, they have provided significant insights into the distribution of blood in the uterus and placenta, identifying features such as uterine 'shunt pathways', that is blood vessels that directly connect arteries and veins, bypassing the placenta (illustrated in Fig. 2). Network models have highlighted the roles of these pathways in interpreting clinical ultrasound,[3] paving the way for more in-depth assessment of the uterus to guide future clinical tools.

As the placenta is structurally so complex, current physics-based assessments of its function make simplifying assumptions to capture function at the scale of interest. However, as imaging techniques and computational power accelerate, the field is exploring more complex physical phenomena within structures representative of the placenta. For example, red blood cells within the circulating blood impact both the nature of blood flow in small vessels (Fig. 5a) and transport biochemistry (as oxygen carriers, red blood cells must be considered in simulations of exchange capacity). In addition, the deformability of the placenta is altered in pathology, but this is rarely considered in simulations of placental function. The compressibility of blood vessels within an elastic tissue may have important functional implications when the uterus contracts over the surface of the placenta.[5]

The placenta is not the only system determining the health of a pregnancy. Maternal adaptations to pregnancy are important, including the capacity to carry a liter per minute of extra blood. The fetus too, grows in response to nutrients delivered from the placenta and adapts when it does not get enough. Physical scientists are beginning to assess maternal and fetal circulatory health via mathematical models and are also developing new tools to non-invasively assess physiology.[5] Maternal and fetal heart rate can be measured at the body surface (with ultrasound or electrodes placed on the stomach) and a trend is for development of wearable devices that could measure ongoing function. There is significant variability in fetal heart rate (and so cardiac output) which impacts on blood delivery to the placenta. Understanding the link between the placenta and the fetal circulation that supplies it with nutrients is an ongoing challenge.

Outlook

The mystery of what makes a healthy pregnancy and childbirth is continually being teased apart by new technologies. This includes well-established medical technologies such as ultrasound and MRI, but also machine learning analyses of imaging and physics-based simulations of the function of the placenta. Simulations enable testing of hypotheses and suggest new avenues for investigation. However, there is still considerable scope for new investigations in this field.

One of the major challenges in simulation of placental function is harnessing the complex geometry of the placenta which emerges across multiple spatial scales. Key avenues for investigation include developing tools for meaningful reductions in complexity and developing new strategies to maximize information density extracted from clinical imaging. Alongside simulation, physics and engineering are providing new tools for sensing placental function (such as body surface measurements of uterine or fetal electro-physiology) and for improving the health of a developing fetus or a newborn via artificial life-support systems. It is likely that these devices and systems could benefit in their design from the results of physics-based simulation. With scientists from multiple disciplines truly working together we should see the evolution of new and improved ways to monitor and improve health in pregnancy.

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