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A multiscale model of placental oxygen exchange: The effect of villous tree structure on exchange efficiency

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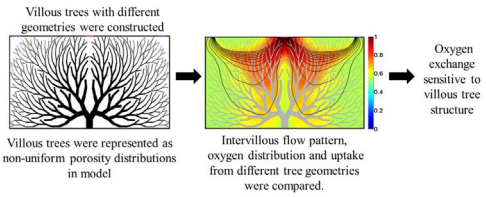
HIGHLIGHTS

- A new oxygen exchange model incorporating a villous tree structure is proposed.
- Key associations between oxygen exchange and villous tree structure are identified.
- Villous tree structure influences intervillous blood flow and oxygen uptake capacity.

GRAPHICAL ABSTRACT



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ABSTRACT

The placenta is critical to fetal health during pregnancy as it supplies oxygen and nutrients to maintain life. It has a complex structure, and alterations to this structure across spatial scales are associated with several pregnancy complications, including intrauterine growth restriction (IUGR). The relationship between placental structure and its efficiency as an oxygen exchanger is not well understood in normal or pathological pregnancies. Here we present a computational framework that predicts oxygen transport in the placenta which accounts for blood and oxygen transport in the space around a placental functional unit (the villous tree). The model includes the well-defined branching structure of the largest villous tree branches, as well as a smoothed representation of the small terminal villi that comprise the placenta's gas exchange interfaces. The model demonstrates that oxygen exchange is sensitive to villous tree geometry, including the villous branch length and volume, which are seen to change in IUGR. This is because, to be an efficient exchanger, the architecture of the villous tree must provide a balance between maximising the surface area available for exchange, and the opposing condition of allowing sufficient maternal blood flow to penetrate into the space surrounding the tree. The model also predicts an optimum oxygen exchange when the branch angle is 24 °, as villous branches and TBs are spread out sufficiently to channel maternal blood flow deep into the placental tissue for oxygen exchange without being shunted directly into the DVs. Without concurrent change in the branch length and angles, the model predicts that the number of branching generations has a small influence on oxygen exchange. The modelling framework is presented in 2D for simplicity but is extendible to 3D or to incorporate the high-resolution imaging data that is currently evolving to better quantify placental structure.

1. Introduction

The human placenta is crucial for the survival and health of a fetus. It is the only exchange interface that provides the fetus with nutrients and oxygen during pregnancy. Numerous pregnancy complications such as preeclampsia and intrauterine growth

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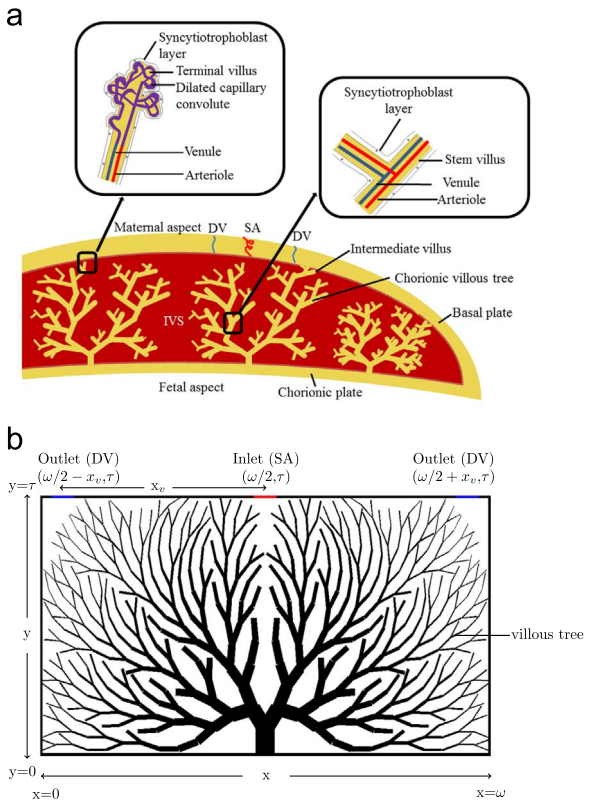

Fig. 1. (a) A schematic diagram of the human placenta at term. The placenta contains numerous chorionic villous trees which stem from the chorionic plate of the placenta into the intervillous space (IVS). Maternal blood enters the IVS from the uterine spiral arteries (SA), percolates through the IVS around the villi before draining through the decidual veins (DV). The fetal circulation resides within the villous trees, and generally runs along the branches in stem and intermediate villi before reaching a dilated and convoluted capillary structure in the terminal villi. Oxygen, nutrients and wastes are exchanged between the maternal circulation and the fetal circulation across the syncytiotrophoblast layer. (b) Model representation of a placental subunit represented by a 2D domain of thickness τ and width ω. Each subunit contains a representative villous tree generated from realistic morphometric parameters fed by a central SA and drained by two DVs. The most distal branches of the villous tree shown are termed intermediate villi, and these villi are assumed to supply 'terminal tissue blocks'.

restriction (IUGR) have been associated with placental malfunction (Regnault et al., 2002). While morphological abnormalities have been identified in pathological placentas (Mayhew et al., 2003; Krebs et al., 1996; Egbor et al., 2006), it is not fully understood how these translate to abnormalities in placental function.

Fig. 1a shows a schematic of placental structure. It contains numerous branching structures known as chorionic villous trees, each of which comprises a network of fetal blood vessels. The largest branches of the villous trees (termed stem and intermediate villi) contain one or more arteriole or venule, and these blood vessels branch along with the villous tree structure. In the smallest villi (terminal villi), dilated capillary convolutes reside close to the villus surface. This surface is covered by a single multinucleated cell layer called the syncytiotrophoblast. The proximity of blood vessels to the surface of the villous tree provides an exchange interface to extract oxygen and nutrients from maternal blood that flows through the intervillous space (IVS) surrounding the villous trees, while keeping the fetal circulation separate from the maternal circulation.

Morphological abnormalities associated with pathology include reduced volume and surface area of terminal villi (Mayhew et al., 2003; Egbor et al., 2006), decreased villus length (Mayhew et al., 2003; Egbor et al., 2006), increased trophoblast epithelium thickness (Mayhew et al., 2003) and abnormally sparse capillary networks (Krebs et al., 1996; Kingdom and Kaufmann, 1997). However, the relationship between these villus abnormalities and the functionality of the placenta is not well defined. Most animal models of the placenta are difficult to extrapolate to human because the placenta displays a wide structural diversity between species (Benirschke et al., 2006). For ethical reasons, it is also impossible to perform invasive experiments or collect measurements directly from the human fetus or placenta during the course of pregnancy. Therefore, although the placenta can be imaged *in vivo* using ultrasound (Pretorius et al., 1998) and magnetic resonance imaging (Sørensen et al., 2013), the resolution of these techniques is currently not sufficient to relate the *in vivo* orientation of villous trees to incoming flow from the maternal spiral arteries, or to extrapolate imaging data to the functionality of the placenta.

In view of the difficulties in directly measuring placental function, there is a need to establish tools to investigate how observed pathologies in villous tree structure influence the functionality of the human placenta. Computational models are emerging as a useful tool to address this problem. Early models of oxygen delivery and uptake within the placenta placed particular emphasis on modelling the exchange of oxygen and carbon dioxide between the maternal and fetal bloodstreams at terminal villi (Hill et al., 1972, 1973). These models include detail on gas uptake dynamics but neglect the spatial flow characteristics of the maternal circulation and its resultant impact on gaseous exchange.

Later models considered maternal flow in the IVS as a porous medium (Erian et al., 1977; Schmid-Schobein, 1988). Erian et al. (1977) modelled the intervillous space in 2D, and assuming that the villous tree is significantly deformed by maternal flow, a flow-dependent tissue permeability was included into their model. Chernyavsky et al. (2010) combined a 3D axisymmetric porous medium approach and first order solute uptake kinetics by a homogenised villous tree (uniform porosity throughout). These porous medium models have predicted 'short-circuiting' of maternal blood flow from maternal spiral arteries to decidual veins when there are highly permeable regions in the vicinity of these arteries and veins (Erian et al., 1977), and when arteries and veins are in close vicinity (Chernyavsky et al., 2010). In this case, there is an effective shunt as oxygenated blood does not circulate around the villous tree before leaving the IVS. This type of model also suggested that greater distances between spiral arteries and decidual veins facilitate nutrient delivery in the IVS. Chernyavsky et al. (2011) employed a simple model of flow and diffusion around distributed point sinks and statistical analysis of 2D placental sections to estimate the potential error incurred in homogenisation of IVS tissue to uniform or slowly varying area fractions. They showed that the accuracy of homogenisation approaches depended on flow characteristics (Peclet and Damkohler numbers), as well as the relative size of intervillous distances and typical pathlengths from spiral arteries to decidual veins. Recently, Lecarpentier et al. (2016) used the Navier-Stokes equations to model blood flow between 'rigid' tissue obstacles in a 2D representation of the IVS. This approach includes significant geometric detail but is computationally expensive so does not lend itself to large scale simulations of blood flow and/or nutrient transport in the whole placenta. Serov et al. (2015), Serov et al. (2015) took a very different approach to simulating placental oxygen exchange, introducing a stream-tube model of oxygen exchange in a placental subunit. This model predicted optimal placental efficiency at tissue volume fraction that corresponds well to those found in normal placentas. Comprehensive reviews of placental exchange models can be found in earlier publications (Chernyavsky et al., 2010; Serov et al., 2015).

Existing placental exchange models are simplified geometrically, either by assuming that the villous tissue is homogenous