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Mini Review

Advances in Human Placental Biomechanics

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ABSTRACT

Pregnancy complications are a major clinical concern due to the related maternal and fetal morbidity. Many are caused through defective placentation, but research into placental function is difficult, principally because of the ethical limitations associated with the *in-vivo* organ and the difficulty of extrapolating animal models. Perfused by two separate circulations, the maternal and fetal bloodstreams, the placenta has a unique structure and performs multiple complex functions. Three-dimensional imaging and computational modelling are becoming popular tools to investigate the morphology and physiology of this organ. These techniques bear the potential for better understanding the aetiology and development of placental pathologies, however, their full potential is yet to be exploited. This review aims to summarize the recent insights into placental structure and function by employing these novel techniques.

Contents

1. Introduction

The placenta is a complex organ that performs a critical function: nourishing a developing baby. It attaches to the uterine wall and connects with the foetus *via* the umbilical cord, growing and adapting during pregnancy to meet fetal demands. Apart from providing the foetus with oxygen, the placenta performs many other vital tasks: for example, it shields the foetus from maternal immune attack *in utero* and fulfils excretory, endocrine, catabolic and absorptive functions [1]. The placenta is the organ that displays most interspecies variation, with the different types sharing only one essential feature: the existence of two separate circulatory systems, the maternal and fetal placental circulations [1].

Studying placental function is far from just an academic exercise. Placental complications can have fatal outcomes for both mother and baby. In fact, 50% of the ~3000 stillbirths in the UK each year result from pregnancy disorders and conditions affecting the placenta [2]. A deficient placental function can result in poor fetal growth which accounts for at least one-third of perinatal deaths in the UK (~1500*per*

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annum). A further 40,000 pregnancies are complicated by fetal growth restriction (FGR) or pre-eclampsia (PE) [1].

Three factors considerably complicate research into the functional morphology and physiology of the human placenta. Firstly, *invivo*research is strongly restricted by ethical constraints, but also by the limits of resolution of the ultrasound scan which is the only imaging test routinely performed during pregnancy. Secondly, *exvivo* research depends on the availability and accessibility of and to the organ, which in turn depends on hospital protocols, number of volunteers, patient history and mode of delivery. Additionally, an *exvivo* placenta needs to be manipulated as soon as it is collected to avoid the collapse of its vascular structure [3]. Lastly, due to species differences in body size, duration of pregnancy, litter size and living conditions, the shape, structure and biochemistry of the placenta differs considerably even among otherwise closely related species [1], limiting the validity of animal models. As a consequence, there is a pressing need for novel and powerful investigative techniques that can uncover the aetiology of pregnancy complications. This article, therefore, summarises the latest developments and knowledge gained through the combination of two emerging technologies that have improved our understanding of placental morphology and function: 3D imaging and computational modelling.

2. Human Placental Morphology

Key to our understanding of the source of pregnancy complications is the full comprehension of placental structure-function relationship in healthy pregnancies.

A typical full-term delivered placenta is a round to oval, flat organ. Its average measurements are 513 g in disc weight [4], 22 cm in diameter, 2.5 cm in thickness at the centre, and has a surface area of almost 15 m^2 [5]. However, there are significant inter-individual variations in these measurements [1]. The placenta has two surfaces, the chorionic plate that faces the baby and to which the umbilical cord is attached, and the basal plate that is apposed to the uterine wall.

Placental shape has been regarded as round or elliptical but functionally unimportant [6,7]. Nevertheless, increased variability of placental shape has been associated with lower placental efficiency, ahypothesis supported by either uteroplacental or feto-placental vascular pathology [6]. A recent study of 2120 women found a relationship between placental surface area and weight, with uterine and umbilical blood flows, both of which are associated with fetal growth rate [8]. Another study of 916 women found correlations between the surface area of the chorionic plate and its perimeter with birth weight [9], suggesting that these comparatively simple measurements can identify suboptimal placental development. Although umbilical cord insertion is assumed to happen at the centre of the chorionic surface, a recent study found that the cord is actually not centred [7]. However, no relation to adverse outcomes was found [7,10].

The chorionic arteries and vein branch from the umbilical cord towards the basal plate creating about 65 villous stems, each then branching into multiple intermediate villi [1]. The villous trees are regarded as the main functional units of the placenta since they represent the principal site of maternal-fetal exchange [1]. Placental villi are commonly differentiated by their calibre, architecture, position and function. However, despite their classification, all villi exhibit the same basic feature: a villous membrane that separates the maternal and the fetal circulations [1]. The villi undergo differentiation throughout gestation resulting not only in different villous types but also in a huge rise of the villous surface area and thinning of the membrane [11,12]. The linear growth of the terminal villi, which begins in the second trimester, results in a reduction of the maternal-fetal barrier to about 4 μm at the vasculosyncytial membrane near term [12].

Due to its functional importance, understanding the role of a terminal villus geometry is crucial to better understand the efficiency of the placenta as an organ of exchange. Many critical aspects of placental transport are unknown: the interconnectivity of the fetal capillary network, the speed and directions of the two involved flows (maternal and fetal), the extent of the feto-capillary structural variability within a placenta and between different individuals, among others. These aspects are fundamental for efficient transport as they enhance diffusional exchange and therefore, abnormalities in the villous tree structure are associated with placental pathologies.

2.1. Three-dimensional Imaging of the Villous Trees

Three-dimensional imaging modalities are emerging as reliable tools to better asses the architecture of the feto-placental vasculature. In fact, by reconstructing light microscopy images, Haeussner etal. [13] demonstrated that placental histology is susceptible to significant inter-individual observations and inaccuracies. Subsequently, different 3D approaches have been proposed to characterise placental villous trees.

In order to investigate the global feto-placental vasculature, micro-computed tomography (μCT) [14] and magnetic resonance angiography (MRA) [15] have been proposed as potential and convenient tools (seeFig. 1d & e, respectively). After evaluating different contrast agents, optimising the imaging protocol and ensuring repeatability, Chen etal. [15] proposed pump oil as an economical and efficient contrast agent for MRA. These techniques allows the visualisation, reconstruction and quantification of up to 6 generations of placental villi. However, if the purpose is to investigate the smaller branches of the villous tree, a more suitable approach would be to use microscopic imaging techniques.

The pioneering works of Jirkovská etal. [16,17] reconstructed thethree-dimensional structure of terminal villi using confocal laser scanning microscopy (CLSM) images (see Fig. 1a). The different feto-capillary loops and their spatial arrangement in normal placentae were revealed, highlighting the potential of this technique; however, no structural analysis was performed. In order to quantify the villous tree geometry, reconstructions from light microscopy were proposed as an efficient tool [18]. Parameters such as branching hierarchy, branching angles, diameters and lengths of the terminal villi can be obtained using this technique (see Fig. 1b) [18]. Plitman Mayo etal. [19] used fluorescent CLSM images to reconstruct the 3D architecture of the feto-capillary network and the villous membrane in terminal villi (see Fig. 1c). Averaged capillary to villi volume and area fractions were found to decrease with the fixation pressure of the fetal circulatory system, in agreement with previous studies [20]. Following the success of fluorescent CLSM, Merz etal. [21] proposed to clarify the tissue prior to imaging to allow a deeper field of view. High-quality images of several villi were obtained by combining the Visikol® HISTO™technique [22] with fluorescent CLSM in healthy samples from 8, 12, 18, 22 weeks and term placentae.

Three-dimensional imaging has also been used to investigate structural differences in pathological placentae. Using CLSM Jirkovská etal. [25] examined the topological and spatial differences between normal and diabetic placentae (gestational diabetes). Although the results were qualitative, more complicated branching patterns and a large number of redundant connections were found in the pathological samples. A subsequent work by the same authors [26] looked at placentae from type 1 diabetes mellitus, and reported that these show amplification of surface area by enlarging the capillary diameters and creating higher branching.

Placentae from FGR have attracted much attention due to their marked difference in size and structure when compared to normal placentae. Three-dimensional light microscopy images showed that the branching angle and tortuosity of the terminal villi was significantly different between normal and FGR samples [18]. Micro-CT has also been tested as an effective technique to analyse the vascular structure of pathological placentae [27]. Significant differences were found between normal and FGR samples. Mainly, the vascular volume fraction was lower and of a similar magnitude in the different areas of the placenta