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Bioengineering aspects of the umbilical cord

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ABSTRACT

The umbilical cord and its constituent tissues: an outer layer of amnion, porous Wharton's jelly, two umbilical arteries, and one umbilical vein, are designed to protect blood flow to the fetus during a term pregnancy. The outer amnion layer may regulate fluid pressure within the umbilical cord. The porous, fluid filled Wharton's jelly likely acts to prevent compression of the vessels. Blood flow is regulated by smooth muscle surrounding the arteries that is intermingled with a collagen based extracellular matrix (ECM). Doppler ultrasound measurements of blood flow within the umbilical cord, and at specific sites within the developing fetus, provide evidence of impaired blood flow in conditions such as preeclampsia. Mechanosensory communication between cells and the extracellular matrix (ECM) may likely result in cords possessing abnormal physical dimensions, impaired hemodynamics, and altered composition within the umbilical cord tissues. Few studies have explored the biomechanics of the intact umbilical cord, with its constituent tissues, from normal pregnancies or abnormal pregnancies, maternal or fetal complications. Here, alterations in the umbilical cord are reviewed concerning anatomical abnormalities, disease, or chromosomal alterations using sonography, Doppler ultrasound, histology, and biomolecular and biochemical analyses. This paper considers how current knowledge of the umbilical cord and its constituent tissues can be used to infer biomechanical function. In addition, the mechanical consequences of structural abnormalities and altered tissue structure or composition are discussed with a specific focus on preeclampsia.

1. Introduction

The umbilical cord is tasked with providing unimpeded blood flow to the developing fetus and has long been recognized through rituals, symbolism and medical science (Fig. 1) [1]. The tissues of the umbilical cord must work to maintain blood flow during fetal grasping, normal movements, and forces of labor, and in the presence of cord abnormalities such as knots or loops. This paper considers the mechanical behavior of the tissues that make up the umbilical cord and how extrinsic influences may alter, and impair, their function.

Surprisingly while the umbilical cord must effectively function in an environment where mechanical forces abound, it is one tissue that has largely been ignored by bioengineers and physical scientists. Few investigations have examined the biomechanical strength, or related properties, of tissues contained within the umbilical cord – or of the intact cord itself. The literature generally lacks normative data that describe how biomechanical function relates to the structure of umbilical cord tissues and the composition of their extracellular matrix (ECM), the main structural framework within many tissues in the body. While much is known about the physical dimensions, anatomy (*i.e.*, structure), histology, and ECM composition, few explicit analyses of mechanical behavior exist. We therefore must rely on assumptions of biomechanical function of the tissues within the umbilical cord and how extrinsic factors may contribute to mechanical behavior.

The umbilical cord, as a conduit for blood flow, changes in physical dimensions and ECM composition with factors such as gestational age, disorders of pregnancy, and genetic abnormality of the fetus. The mechanical and hemodynamic consequences of such alterations are poorly understood. For example, alterations in blood flow are known to correlate with significant changes in the stiffness and, consequently, the function of cardiovascular tissues with varying forms of adolescent and adult hypertension [2,3]. However, the implications of hypertension in the preeclamptic or growth-restricted fetus have been examined mainly from a biomolecular, biochemical, or a clinical perspective. The umbilical cord is an extension of the fetal cardiovascular system and therefore has great potential for use in studying changes within the fetal vascular tissues.

While the umbilical cord may provide unique insight into alterations that occur within the developing fetus, the prognostic

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Fig. 1. Carving of baby grasping umbilical cord on the Temple of the Frescoes located in the ancient Mayan ruins of Tulum, Mexico. Umbilical cord motifs were common and are thought to symbolize genealogical continuity [62]. Photo courtesy of Audrey Earnshaw (2008) [1].

value of the cord has yet to be fully realized. Advanced computational models have potential as translational tools to enable real-time assessment of fetal health. Postnatal or post-mortem analysis of the umbilical cord may aid in our understanding of how and why cord accidents occur. Combining bioengineering with biochemical and biomolecular analyses may reveal therapeutic targets for a variety of disorders in pregnancy. This review is intended to initiate discourse and research from a multidisciplinary approach to better understand the biomechanical role of the umbilical cord and its constituent tissues with the ultimate goal of stimulating new, multidisciplinary research directions and to ultimately improve pregnancy outcomes.

1.1. Structure of the umbilical cord and its constituent tissues

A normal umbilical cord contains two arteries and one vein surrounded by Wharton's jelly (WJ), a porous connective tissue, and an outer, single cell layer of amnion. The umbilical vessels differ in structure and function as compared to the major vessels in the body. The two umbilical arteries coil around the vein in a helical fashion. Blood flows in a pulsatile manner from the fetus to the placenta through the arteries. A small pulse remains in the more passive transfer of blood back to the fetus through the umbilical vein.

The umbilical arteries do not possess an internal elastic membrane and contain little elastin, in general, while the vein contains an elastic subintimal layer (Fig. 2). Collagen, a mechanically stiff protein, typically serves to limit radial vessel distension at high loads [4]. Elastin, by contrast, is highly extensible at low loads [5]. Within most arterial tissues, the elastic fibers are bound together into fenestrated sheets that exhibit a near perfectly elastic mechanical response [6]. Elastin therefore functions to provide the recoverable, elastic extensibility and subsequent contraction in arteries during pulsatile blood flow [7]. Smooth muscle cells lie throughout the arterial media and participate in regulating muscular tone and eliminate the need for substantial elastin content.

The arteries lack an adventitia of the form that is observed in cardiovascular vessels. Instead, the rigid Wharton's jelly performs the function of the adventitia. The Wharton's jelly consists of a porous, ECM-based backbone and ground substance. This fibrous, porous scaffold is made of collagen and elastin fibers and likely contributes to the firmness of the intact cord. The pores within the Wharton's jelly form canalicular structures that house the proteoglycans, hyalauronic acid (HA), and other molecules that interact with water to form a highly viscous, mucoid fluid. The thickness and turgidity of the Wharton's jelly varies with the expansion and contraction of the vessels and may structurally support and prevent overdistension of the vessels (Fig. 3). Myofibroblasts, cells possessing ultrastructural characteristics of both fibroblasts and smooth muscle cells, within the Wharton's jelly form collagen and other proteins and may actively contract to assist in regulating umbilical blood flow [8]. The endothelial cells that reside within the arteries and vein are unusually rich in organelles that may play a role in amniotic fluid formation [9]. The amnion is structurally comparable to that found in the fetal membranes and may actively maintain fluid pressure in the Wharton's jelly [10].

1.2. Mechanical behavior of the umbilical cord and its constituent tissues

The majority of publications examining umbilical cord tissue biomechanics have examined intact, excised sections of umbilical cord under tensile loading [11-13]. The umbilical cord is seldom

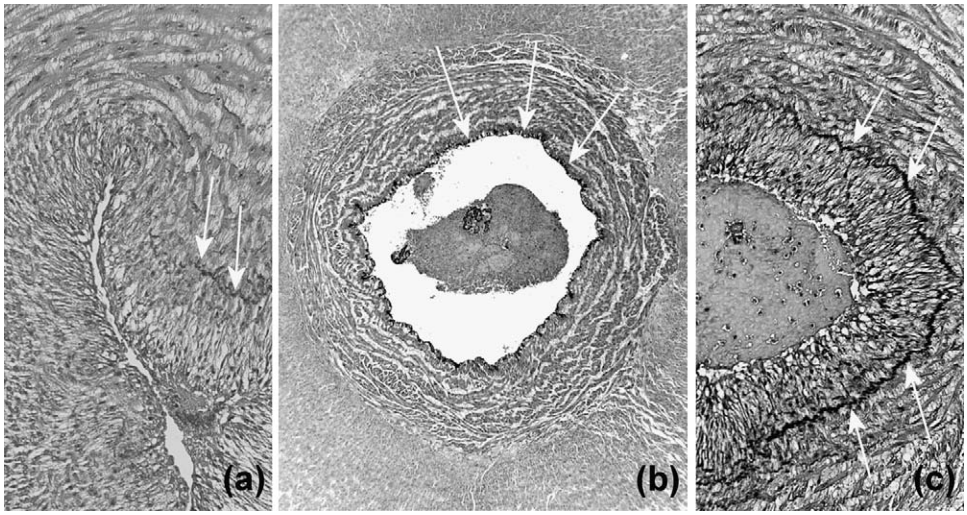

Fig. 2. Umbilical cord sections showing: (a) an umbilical cord artery at 20× and (b) vein at 5× from a normal, term pregnancy and (c) an umbilical artery at 20× from a severely preeclamptic, term pregnancy. An elastic Verhoeff's Van Giesen (EVG) stain shows regions of elastin as dark (denoted by white arrows) in the subintimal layer of the vein and within the media of the arteries. The elastin staining in the preeclamptic artery is much more pronounced than in the normal artery.