What is the placenta?

Graham J. Burton, MD, DSc, FMedSci; Eric Jauniaux, MD, PhD

Aberrations of placental function are widely recognized as having immediate consequences for the outcome of a pregnancy and more recently for influencing the life-long health of the offspring. There is thus an urgent need for research into the organ, but what exactly is the placenta that we should be studying?

Although on a superficial level the human placenta is readily recognizable as the discoid structure that interfaces with the mother, it is in fact remarkably difficult to define biologically. For one thing, no organ can match the placenta for the diversity of its functions because it performs the actions of all the major organ systems while these differentiate and mature in the fetus. For another, there is an astonishing range of morphological variations in placental types seen across mammals and even lower orders.[1]

In his seminal monograph on comparative placentation, Mossman attempted to simplify matters by stating that "the normal mammalian placenta is an apposition or fusion of the fetal membranes to the uterine mucosa for physiological exchange."[2] It is clear from this widely quoted statement that the placenta has 2 components, a fetal and a maternal one that must interact successfully for a healthy pregnancy.

Although this is easy to appreciate this combination in a species that has a noninvasive, epitheliochorial placenta, such as the sheep, it is less easy in the hemochorial situation in which the maternal epithelium has been eroded. What is the maternal component of the human placenta and where is the maternal-placental interface? Recent advances are challenging some of our preconceptions of what the placenta is, and this review touches upon new ideas and areas of uncertainty of significance for contemporary obstetrics and placental research.

According to Mossman,[2] the maternal component of the human placenta must be the endometrium, which undergoes transition to form the decidua in early pregnancy. Although only a few layers of decidual cells are incorporated into the basal plate of the placenta and are often considered as maternal contaminants following delivery, placental development and function is normally inextricably linked with the endometrium. Whereas it is true that the placenta can attach and sustain a fetus for several months at various ectopic sites, trophoblast invasion is often unregulated and the maternal-placental interface severely disorganized outside the intrauterine environment.

Implantation in the human is typically described as a highly invasive process, during which the conceptus becomes completely embedded within the superficial endometrium. Tongues of syncytiotrophoblast do infiltrate between the uterine epithelial cells, but there is increasing evidence that the endometrial stromal cells play an equally active role, sweeping around to encapsulate the conceptus. Hence, the embedded conceptus continues to protrude into the uterine lumen following implantation.

Development of the placenta is precocious because the organ must be ready and able to support the fetus. Villous precursors cover the entire surface of the chorionic sac toward the end of the third week after conception. It is now established that fetal organ development and growth during the first trimester of pregnancy occur in a physiologically low oxygen microenvironment, stimulated by secretions from the endometrial glands that are rich in nutrients and growth factors.[3]

Data from other species demonstrate that the placenta is able to stimulate its own development by signaling to the glands to up-regulate the secretion of what are generically referred to as uterine milk proteins.[4] Although there is no firm evidence yet that this occurs in the human, the hypersecretory morphological change seen in the glandular epithelium during early pregnancy, the Arias-Stella reaction, provides indirect support for this fascinating concept. We do know that maternal glycoproteins in the secretions are taken up by the syncytiotrophoblast, in which they enter the lysosomal digestive pathway and presumably fulfill the nutrient requirements of the conceptus.

In the absence of an effective chorionic circulation at this stage of pregnancy, it is unclear how the nutrients reach the embryo. Amino acids accumulate within the fluid in the extraembryonic coelom, and the recent identification of specific transporter proteins on the outer surface of the secondary yolk sac raises the possibility that this structure, largely considered vestigial, plays an important role in transport in the early stages of human development.[5] Hence, the early, primitive human placenta may function physiologically as a choriovitelline placenta, in common with those of many mammalian species,[1] although morphologically it never develops as such.

Given this newly identified reliance on the gland secretions, there is a need to assess whether failure of 1 or more steps in the placental-endometrial dialogue may underpin some complications of pregnancy. It is notable, for example, that the placenta grows more slowly during the first trimester in pregnancies that subsequently miscarry or go on to display growth restriction than in normal cases.[6]

From the Centre for Trophoblast Research, Department of Physiology, Development, and Neuroscience, University of Cambridge, Cambridge, UK (Dr Burton), and Academic Department of Obstetrics and Gynaecology, Institute for Women's Health, University College, London, UK (Dr Jauniaux).

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Corresponding author: Professor G. J. Burton, MD, DSc. gjb2@cam.ac.uk

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Toward the end of the first trimester, the primitive placenta undergoes remodeling to form the definitive organ and the smooth membranes. This process is associated with the onset of the maternal arterial circulation and is mediated by locally induced oxidative stress because of the concomitant rise in oxygen concentration.[3] These morphological changes are a reflection of millions of years of adaptation to changes in oxygen concentration in the earth's atmospheric environment.

The absence of a continuous maternal circulation inside most of the primitive placenta during the first trimester placental barrier is essential to control the oxygen levels inside the gestational sac during organogenesis. It also adds to the natural defense of the fetus against parasites and viruses when it is at its most vulnerable.

Recent changes in human environmental habitats caused by pollution, habits such as smoking, and the increased use of medical and recreational drugs have challenged the concept of a natural protective role of the placental barrier. The thalidomide and diethylstilbestrol teratogenic catastrophes tragically illustrate its limitations. By contrast, recent data from metagenomic sequencing show that the placenta is frequently colonized with maternal commensal bacteria during pregnancy and indicate the selective role of the placental barrier and indirectly its additional metabolic and immune contributions to the developing fetus.[7] More knowledge in this area is essential to better understand our interaction with the terrestrial environment in which placental mammals have evolved over the last 225 million years.

The onset and subsequent development of the uteroplacental circulation is dependent on the conversion of the endometrial spiral arteries from highly contractile muscular arteries into flaccid, dilated conduits. Extravillous cytotrophoblast cells play a key role in this process and migrate from the tips of the placental anchoring villi into the wall of the uterus as far as the inner third of the myometrium.

This deep invasion appears to be a uniquely human phenomenon among higher primates and challenges our perception of the physical extent of the placenta. It is clearly not the basal surface of the delivered placenta, which is a mix of fetal trophoblast and maternal decidual and endothelial cells embedded in a fibrinous matrix.

The interactions of the extravillous trophoblast cells with the maternal innate immune system are also challenging our understanding of the maternal-fetal immune dialogue underpinning pregnancy. It is now evident that a degree of activation of the uterine natural killer (uNK) cells is essential for a successful outcome and that this depends on the combination of HLA-C ligands on the trophoblast cells and killer immunoglobulin-like receptors expressed by the uNK cells.[8]

Far from killing trophoblast cells, the uNK cells appear to encourage migration of the extravillous trophoblast cells into the endometrium. Their release of cytokines and growth factors in response to activation is thought to mediate the arterial conversion. The conversion has a profound impact on the velocity and the constancy of maternal blood flow into the placenta[9] and is a key, but hidden, aspect of placental development.

Further challenges to our understanding of the location of the maternal-placental interface arise through a new appreciation of deportation of cells and particles from the placenta. It has long been known that fragments of placenta, in particular aggregates of syncytial nuclei, break off from the villous tree and are swept into the maternal circulation. Most become lodged in the capillary bed of the lungs in which they appear to stimulate no local reaction, leading to the perception that this is a passive process. However, it is now realized that these aggregates are transcriptionally active and may play an important role in maternal-fetal signaling.[10] They also carry retroviral proteins that potentially have immunomodulatory properties.

The situation has become even more complex since the recognition that the placenta releases large quantities of exosomes into the maternal circulation from early pregnancy onward.[11] These nanovesicles are highly stable and contain a wide array of proteins and microribonucleic acids that may mediate signaling to the maternal endothelium, organ systems, and immune cells. Hence, we need to think beyond traditional endocrinology when considering the influence of the placenta on maternal physiology. Furthermore, the exosomes provide an opportunity to obtain a minimally invasive biopsy of the placenta that could provide insight into its well-being.

We have thus come far from the immunological paradox posed by Medawar[12] in 1953, comparing the placenta with an allograft. Indeed, it appears that interactions between placental cells and the maternal immune system have evolved to perform more physiological than classical immunological functions. Nonetheless, the placenta does represent an immunological shield for the fetus because the absence of class I and II HLA antigens renders the surface of the villous trees immunologically inert.

The definition of Mossman[2] emphasizes transport as the main purpose of the placenta. Whereas exchange is undeniably highly important, the definition fails to recognize the organ's other facets. For example, transport is selective and in general the placenta either excludes or renders inactive maternal hormones and xenobiotics to allow the fetus to develop in a safe and independent milieu.

The placenta is also a major endocrine organ, secreting more than 100 peptide and steroid hormones that modulate maternal physiology. Early in pregnancy these promote the accretion of maternal nutrient reserves that are mobilized later for fetal use and lactation. Placental lactogens and growth hormone exert antiinsulin effects and promote lipolysis, boosting maternal glucose and free fatty acid concentrations for exchange to the fetus. Indeed, the placental production of growth hormone is so powerful that secretion from the maternal pituitary is suppressed by midpregnancy. Hormones such as erythropoietin and angiotensinogen mediate maternal cardiovascular and other adaptations.