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Animal Models to Study Placental Development and Function throughout Normal and Dysfunctional Human Pregnancy

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Abstract

Abnormalities of placental development and function are known to underlie many pathologies of pregnancy, including spontaneous preterm birth, fetal growth restriction and preeclampsia. A growing body of evidence also underscores the importance of placental dysfunction in the lifelong health of both mother and offspring. However, our knowledge regarding placental structure and function throughout pregnancy remains limited. Understanding the temporal growth and functionality of the human placenta throughout the entirety of gestation is important if we are to gain a better understanding of placental dysfunction. The utilization of new technologies and imaging techniques that could enable safe monitoring of placental growth and function *in vivo* has become a major focus area for the National Institutes of Child Health & Human Development, as evident by the establishment of the "*Human Placenta Project*". Many of the objectives of the *Human Placenta Project* will necessitate pre-clinical studies and testing in appropriately designed animal models that can be readily translated to the clinical setting. This review will describe the advantages and limitations of relevant animals such as the guinea pig, sheep and non-human primate models that have been used to study the role of the placenta in fetal growth disorders, preeclampsia or other maternal diseases during pregnancy.

Keywords

Animal models; Human Placenta Project; Placenta Development and Function; IUGR; Preeclampsia

INTRODUCTION

The placenta is pivotal not only to studying normal maternal-fetal biology, but also in deciphering fetal growth disorders, preeclampsia or other maternal diseases and subsequent predisposition to lifelong illnesses[1–4]. Assessment of placental structure, development and function throughout pregnancy in humans represents difficult challenges due to the need to avoid risk to the mother and fetus[5]. Most information on human placental biology has been obtained by studying placental tissue obtained after delivery, often from pathological pregnancies at various stages of disease, from term deliveries in which placental

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development has already peaked or began to degenerate, or from *ex vivo* model systems[6–9]. There is a paucity of information obtained earlier in gestation when many pregnancy pathologies have their origin, as well as limited information on the normal trajectory of human placental development and function[5]. A better understanding of the maternal-feto-placental functional dynamics throughout the entirety of gestation could lead to both preventative and therapeutic interventions with lifelong impact[4].

The overarching goals of the *Human Placenta Project* are to improve current clinical methods and develop new technologies for the real-time assessment of placental development and function across normal and abnormal pregnancies; to evaluate non-invasive biomarkers for the prediction of adverse pregnancy outcomes; and to understand the contributions of the placental to long-term health and diseases for both mother and offspring[4, 5]. A number of specific focus areas include, the anatomic and structural changes of the placenta across gestation; villous cell structure and function; blood flow, oxygenation, diffusion and perfusion within the placenta; maternal-fetal nutrient transfer; metabolic changes (oxygenation, oxidative stress, lipids and lactate); response to environmental stresses; regulation of maternal and fetal immunologic function (outlined in RFA-HD-15-030; RFA-HD-15-030; RFA-HD-15-034). To adequately address these focus areas pre-clinical studies in appropriately designed animal models is clearly needed.

This review will provide a brief overview of clinically relevant animals models that have previously been used to study fetal growth disorders, preeclampsia or other maternal diseases during pregnancy. The advantages and limitations of the guinea pig, sheep and non-human primates will be discussed and compared to rodents (mouse, rats) where appropriate, in order to demonstrate that these animal models serve as valuable research tools for enhancing our understanding of placental biology, underlying pathologies and patient management strategies.

Anatomy of the Placenta Across Species

Vital for pregnancy, the placenta performs multiple functions to ensure an optimal environment for offspring survival and is unique in that it acts as the lungs, kidneys, and liver, and the gastrointestinal, endocrine, and immune systems for the fetus. It also produces hormones to help maintain pregnancy, support fetal development, and protects the fetus from the maternal immune system. Normal embryonic development is dependent upon sufficient oxygen, nutrient and waste exchange through the placenta[10], however the way in which the placenta achieves this varies among species[11–13].

The placenta has been categorized in mammals based on the gross shape, histological structure of the maternal-fetal interface and the type of maternal-fetal interdigitation[12, 14–16]. There are four main placenta types recognized by gross morphology and whether the maternal-fetal exchange area is found over all the available surface of the chorionic sac or whether it is restricted; *Diffuse* (horses, pigs), *Multicotyledonary* (ruminants), *Zonary* (carnivores), *Discoid/Bidiscoid* (primates, rodents, rabbits). In addition, the placenta is further subdivided according to the cell layers compromising the interhemal area; *Epitheliochorial* (horses, pigs and ruminants), *Endotheliochorial* (carnivores) and

Hemochorial (rodents, rabbit, primates)[12, 15, 16]. For more detail on comparative placentation between species, see previously published reviews[12, 14–16].

The fundamental steps necessary for successful placentation include, trophoblastic invasion, vascularization of the trophoblast to establish and maintain feto-placental vasculature, and subsequent maternal vascular remodeling to gain utero-placental circulation[10, 17, 18]. In most species (other than primates) the trophoblast is simply apposed to the uterine epithelium without any or minimal destruction of the maternal tissue (e.g., epitheliochorial or endotheliochorial implantation)[10, 18–21]. Thus, there is no direct contact of maternal blood with fetal tissue. Further invasion that occurs in human placentation leads to erosion of maternal vessels, so that the trophoblast is bathed directly by maternal blood (hemochorial placentation)[18]. The barrier between the fetal and maternal blood is very thin, making the exchange of oxygen and nutrients very efficient. The depth of trophoblast invasion and maternal vascular remodeling varies among primates; with the deepest invasion of the trophoblast and a nearly complete digestion of maternal vessels is found in humans[22].

Non-human Primate

Higher order primates remain the most closely aligned to humans in terms of pregnancy in a number of ways; a longer gestational length than rodents and ruminants, lack of maternal serum progesterone withdrawal, regulation of steroidogenesis within the placenta, unicornuate uterus, and uterine contractions[13, 23–25]; Ellinwood, 1989 #1660;Mitchell, 2009 #1608}. Old world monkeys (e.g., Rhesus macaque, Baboon) have been used to model human parturition[26, 27], implantation and placentation[28], and endometriosis[29–31] for decades. The bidiscoid hemochorial placenta of rhesus monkeys occurs in about 90% of term gestations while the remainder has a single lobe[28, 32]. The umbilical cord attaches centrally to the primary lobe, while placental bridging vessels extending from the umbilical cord course over the primary disc to distribute to, and within, the structurally independent secondary lobe[33]. The rhesus placenta has a villous structure the same[28, 34]. Although trophoblast invasion is considered superficial against the depth of invasion seen in the human placenta, the nature of the interhemal barrier is analogous and the pattern of circulation in intervillous space is comparable to humans[34].

Guinea Pig

The guinea pig has an epitheliochorial and diffuse type of placenta. In the interhemal barrier, maternal and fetal vessels are situated below the basement membranes of the endometrium and trophectoderm without destruction of the endometrial tissue[35]. In most experimental animal models, there is an abrupt withdrawal of progesterone from the maternal circulation before parturition[36]. Only in the guinea pig and human are progesterone levels maintained at a high and increasing concentration throughout parturition. As in the human, parturition in the guinea pig occurs when maternal progesterone concentrations are high and rising[37]. The ovary is the major source of progesterone for the first 4 weeks following conception, and then the placenta becomes predominant for the remainder of pregnancy[38, 39]. This luteo-placental shift is remarkably similar to what occurs in human pregnancy[40, 41]. Luteal progesterone secretion appears to decline after days 35–40, and there is an accompanying significant fall in plasma progesterone concentration[38, 42].

Sheep

Sheep are phylogenetically distant from primates and the anatomical structure of their placenta is very different to humans[20]. Ruminants have a cotyledonary, epitheliochorial placenta, but because the uterine epithelium is modified by invasion and fusion of binucleate cells, its structure is generally referred to as synepitheliochorial. Although sheep have a long gestation, deliver precocial young and are amenable to invasive procedures during pregnancy, there are some striking differences to humans. The interhemal barrier of the sheep placenta is one of the most superficial implantations, thus lacking significant trophoblast invasion of the uterus[43]. In contrast, there are notable similarities; the villous tress of the sheep cotyledon is structurally similar to that of the human placenta[43]. While the sheep might be less than ideal for the human, the similarity in fetal placental vascular structure allows the sheep to serve as a useful model for placental vascular development and nutrient exchange[20].

Choice of Animal Models

Utilization of suitable animal models that are easily translatable to the clinical setting is needed to investigate many of the poignant questions raised by the *Human Placenta Project*. As to which animal model is best suited for studying human placentation and pregnancy continues to be debated. Several reviews continue to raise concerns in relation to the validity of using experimental animals to model human pathologies, in particular, human pathologies of a complex and multifactorial nature such as placental dysfunction[44–46]. Among investigators, there are often biases towards one animal model over another based on availability, housing conditions or financial considerations and not necessarily scientific merit. Obviously it is important to consider these constraints, but one may inadvertently overlook a more appropriate model or the possibility of multiple animal models that can address the questions being investigated. We propose that there is no “single ideal animal model” for studying human parturition, placenta dysfunction, fetal growth disorders or preeclampsia. All models have their advantages and limitations. Consideration of a particular animal model due to the development trajectory or type of placentation may be well suited to one avenue of study but not to others. For example, when investigating the processes of spiral artery remodeling and the association between impaired invasion and pregnancy complications such as preeclampsia, the animal of choice should ideally have similar depth of trophoblast invasion compared to humans. Although the closest models to human are found among non-human primates, the equivalent depth of invasion seems to be only evident in chimpanzees and gorillas[47, 48]. Due to their endangered status and government sanctions the feasibility of these animals as models for research is highly limited. Cultured trophoblast *ex vivo* explants of human spiral arteries and villous explant cultures on decidual tissues have elucidated mechanisms of trophoblast-associated spiral artery remodeling, trophoblast induced apoptosis in the endometrium and the vascular smooth muscle as important elements in these vascular changes[44, 49, 50]. However, despite the practicality of *ex vivo* studies, to gain a real appreciation for the relationship of spiral artery remodeling to placental function and fetal development throughout gestation, *in vivo* animal models are still warranted.

Despite the superficial implantation and a less developed decidua with little interstitial trophoblast invasion of the rhesus monkey and baboon[15, 16], these animals provide unparalleled opportunities to study placenta permeability, nutrient transfer and pharmacodynamics of new therapeutic drugs. Rhesus monkeys are amenable to a number of manipulations during pregnancy including, chronic catheterization for simultaneous sampling of the maternal-fetal and inter-uterine compartments[51, 52], inter-uterine placental ligation as a model of placental insufficiency and IUGR[33], as well as nutritional manipulated pregnancy models to explore the fetal-placental origins of adult disease[2]. Similarities exist with uterine and placental anatomy, gestational length (~168 days), electromyographic activity, singleton pregnancies, and the ability to directly compare fetal and neonatal development to humans is unparalleled. Unlike rodents who are born immature in terms of brain maturation, the rhesus neonate has significantly more white matter at birth, making the rhesus a far better model for assessing neonatal cognitive and behavioral outcomes as a result of adverse pregnancies (e.g., placental insufficiency, fetal growth restriction and preeclampsia)[53, 54]. The permeability and placental transfer mechanisms in the rhesus are analogous to human placenta, thus the efficacy, safety, and pharmockinetic-pharmocdynamics of new therapeutic drugs are routinely tested in the rhesus macaque prior to clinical use[55–58]. Spontaneous preeclampsia has been documented in the rhesus macaque (personal observations)[59] and experimentally induced preeclampsia is achievable in baboons in which all the clinical hallmarks of human preeclampsia are present (e.g., hypertension, proteinuria, renal histological changes)[60, 61]. It is however, appreciated that financial and ethical considerations precludes the widespread use of these precious animals and is limited to specialized facilities across the country (e.g., National Primate Research Centers). It is now an opportune time for multi-disciplinary collaborative efforts to emerge between placentologists and primatologists located at various National Primate Centers, in particularly those that specialize in reproductive and developmental sciences (e.g., Oregon National Primate Research Center; Southwest National Primate Research Center). Data garnered from non-human primate and baboon studies have been tremendously informative of parturient events[26, 62], and their influence in part enhanced by the deficiencies inherent in other animal models.

The seminal work of Liggins and colleagues unraveled key details of the regulation of parturition in sheep and established the basic concepts of parturition in this species, leading to a greater understanding of fetal physiology throughout pregnancy[63–66]. Obvious advantages are similar to those outlined for non-human primates in the context of experimental manipulations, however the ovine model has major discrepancies in the endocrinology of parturition compared to humans, which can limit its usefulness for studies of placental development and function[36]. Firstly, the dependence on progesterone withdrawal for initiating labor and placenta steroidogenesis are markedly different in the ovine placenta to that of humans[37]. Secondly, the pivotal role of the fetus in determining the end of parturition is not the case in human pregnancy.

The guinea pig is a great alternative to other rodent species and is among the few known to develop toxemia[67]. The guinea pig is a well-established model for the study of placental transfer[68] and fetal growth restriction[69, 70] due to the similarities to human placentation. Guinea pigs deliver precocial young after a relatively long gestation, thus many events that

occur during human fetal development also happen during fetal life in guinea pigs[19], where as this is in contrast to rodents who deliver altricial young and many developmental processes happen during postnatal life.

Advantages for the commonly used laboratory animals (rats) include hemochorial placentation, easy housing conditions, economically affordable and a short gestational length (20–22 days) vs. human (~266 days). There are also a number of challenges with the use of rodent models. Although a short gestational length is advantageous in some circumstances, it also limits the ability to maintain maternal-ftal catheters precluding them from longitudinal analyses. Their anatomical size can make it challenging to perform real-time monitoring of placental development and function (e.g., ultrasound, MRI). Maternal blood is delivered to the placenta via only two to three spiral arteries; which is in sharp contrast to non-human primates and humans[44].

New Modalities for Placental Vascular Imaging

Our understanding of the mechanisms involved in normal placental growth and function are limited, in part by the lack of imaging modalities that facilitate the study of both normal and abnormal pregnancy, as highlighted in the *Human Placenta Project*[5]. Ultrasound in all its modalities (e.g., B-mode, color, power and spectral Doppler, 3D/4D and contrast-agent enhanced), is unquestionably the most preferred method of examination in the clinically setting, but it is not without limitations[71–74]. Some drawbacks of using Doppler to measure fetal-placental blood flow are that it tends to rely upon operator skill, signal postprocessing and insonation angle[75]. Contrast-enhanced ultrasound imaging strategies have been reported for characterizing intervillous blood flow[76, 77], unfortunately this technique is not capable of characterizing the entire placenta due to restrictions in the achievable field of view[78].

Magnetic resonance imaging (MRI) is currently used in human pregnancies typically to evaluate fetal abnormalities and in some instances to evaluation abnormal placentation[79–81], yet the use of MRI to measure placental perfusion in humans is limited[78]. There have been limited studies using MRI in conjunction with diffusion weighting, arterial spin labeling, and manipulation of oxygen concentration to create blood-oxygenation-level-based contrast to characterize maternal placental vascular structure[82–87], but these methods currently have not provided spatial and quantitative characterization of the maternal perfusion of the placental intervillous space[78].

In line with the *Human Placenta Project*, Frias and colleagues have recently described a novel application of Dynamic Contrast-Enhanced MRI (DCE-MRI) for the analysis of maternal perfusion of the non-human primate placenta[78]. This DCE-MRI protocol quantified blood flow within individually identified cotyledons, and produced three-dimensionally maps the placental structure in a way that is consistent with the placental histopathologic structure[78]. Due to the characteristic organization of the maternal vasculature, gadolinium-based contrast reagent (CR) mediated signal enhancement enabled the delineation of spiral artery perfusion of maternal blood to the placental intervillous spaces following intravenous administration of a standard CR. In a number of animal studies[88, 89] and perfused human placenta[88], CR-mediated magnetic resonance signal

enhancement has been used to study maternal perfusion of the placenta, however these studies did not provide quantitative 3D analyses to determine perfusion domain boundaries and intervillous flow[78].

CONCLUDING REMARKS

Whilst many individual aspects of placental growth and function (i.e., growth factors, nutrient transport, oxygen transfer, blood flow regulation) can be studied in the laboratory, only a few components can be measured "risk-free" or non-invasively in a real-time clinical setting. To make a significant impact on our ability to detect adverse pregnancy outcomes, and to monitor the temporal development and function of the placenta in normal and abnormal pregnancies, continued study of the molecular mechanisms indicative of placental dysfunction as well as the functional aspects will require the use of appropriate animal models. Ultimately the requirements for a better animal model should include the following; (1) Progesterone should be produced predominantly in the placenta, and withdrawal of progesterone from the maternal circulation should not be the critical stimulus to parturition, (2) The transition from uterine quiescence to activation should occur over a time span sufficient to facilitate longitudinal assessments, repeated sampling protocols and advanced imaging techniques, and (3) a corresponding type of placentation. It is hoped that the *Human Placenta Project* will facilitate new collaborative efforts for multi-disciplinary teams such as biologists, physiologists, placentologists together with primatologists to further understand the complexity and consequences of placental diseases.

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