

## Concept Clearance

**Branch:** Population Health Branch

**Council Period:** 201510

**Concept Title:** Environmental influences on Placental Origins of Development (ePOD) Concept

### Introduction

The placenta is the least understood human organ and arguably one of the more important, not only for the health of a woman and her fetus during pregnancy but also for the lifelong health of both. The placenta connects the developing fetus to the uterine wall and functions as a barrier to mediate nutrient uptake, waste elimination, and gas exchange via the mother's blood supply. It helps fight against internal infection, produces hormones to support pregnancy and metabolic activity, and transports environmental chemicals both within the placenta and to the fetus. Yet, our understanding of placental physiology, endocrinology and toxicology is very limited. It is becoming clear that the placenta is more than a conduit between mother and fetus. It is a physiologically active tissue, which has the potential to impact the health of the fetus and the mother.

The Environmental influences on Placental Origins of Development (ePOD) initiative aims to accelerate the development and application of innovative models and approaches for placental exposure assessment as well as to better understand the effects of environmental chemicals on early stage placental physiology, endocrine and metabolic functions, including subsequent effects on fetal development.

The structure, including size, shape and orientation, and function of the placenta not only affect the health of the mother, as seen in the development of insulin resistance, preeclampsia, gestational hypertension, and eclampsia, but also affect the fetus, causing premature birth, interuterine growth restriction (IUGR), and functional changes in the fetus including altered male reproductive development and neurodevelopmental abnormalities. A variation of DOHaD termed "placental origins of health and disease", stems from studies where disturbances in placental development affect maternal-fetal exchanges, and thus the development of systems linked to later-life diseases.

The human placenta is a sexually dimorphic endocrine organ capable of metabolizing and synthesizing steroid hormones, which are necessary for trophoblast development, embryonic implantation, maintenance of pregnancy, and fetal growth, development and well-being. Placental cells contain transporters and enzymes responsible for protecting the fetus from toxins/toxicants, however, we understand very little about their mechanisms of passage or the effect of exposures on placental and fetal development. These processes are particularly important to understand during the first trimester of pregnancy when the fetus lacks its own metabolic machinery and is undergoing substantial organ development.

A growing literature suggests that environmental inputs to the placenta play a major role in determining the trajectory of placental development and functional sufficiency. Potential environmental sources of placental dysfunction may be readily quantified into discrete physical entities such as environmental chemicals, or they may be of a more general nature such as exercise, maternal diet and nutritional status, BMI or level of stress. These environmental factors may act directly on the placental cells or indirectly by altering the mother's physiology. Understanding the role of environmental factors on placental development will be essential to crafting strategies that optimize the chances for a successful pregnancy outcome.

Assessment of the placenta presents special challenges due to the need to avoid risk to the mother and developing fetus. Thus, most information on human placental biology is obtained by studying placental tissue obtained after delivery, often from pathological pregnancies such as preterm deliveries occurring predominately in the third trimester, from term deliveries in which placental development has already crested, or from in vitro model systems. There is a paucity of information obtained earlier in gestation when many pregnancy pathologies have their origins.

### Research Goals and Scope

We propose a two-phase concept that includes pursuing collaborative opportunities with the NICHD-lead Human Placenta Project (HPP), and development of a cross disciplinary NIEHS-led program aimed specifically at understanding the effects of environmental exposures on early stage placental health and their effects on fetal health.

The HPP aims to improve methods for monitoring placenta development in real-time, to develop tools and technologies and non-invasive markers to predict problem pregnancies, and to understand the contributions of placental development to long term health and disease. We plan to work collaboratively with NICHD to integrate NIEHS research opportunities with respect to better understanding the role of the environment in the relationships among placental, maternal, and fetal health during early pregnancy.

Currently, epidemiological studies lack sensitive and specific methods to assess real time placental exposures and to study

chemically induced placental damage in early pregnancy. Some rely on maternal urinary biomarkers, such as placenta-derived hormones, to assess exposures in placental and fetal tissue, while others measure placental health based on morphometric scores of term placentas. Thus it is important to establish biomarkers to identify chemically-induced placental effects of exposure during pregnancy to predict complications such as preterm birth.

Human placentas are unique; therefore there is not one animal model ideal for studying human placentation. Species differences in gestational development and trophoblast invasion highlight the need to establish better model systems to study placental development and to develop predictive biomarkers of placental exposures and toxicity. Studies are also needed to determine chemical effects on early stage placental metabolic enzymes, transporters, receptor signaling pathways, endocrine functions, toxicant metabolism, gene and protein expression and epigenetic changes. These studies will help us better understand which chemicals can alter placental function, when they act, their mechanism of action, and whether they can alter normal development.

### Mechanism and Justification

We propose a multicomponent program designed to fill specific and critical needs to address environmental influences on placental development. These will include collaborative grant opportunities with NICHD's Human Placenta Project and NIEHS funding opportunities to develop a cross-disciplinary program aimed specifically at understanding the effects of environmental exposures on early stage placental health and their effects on fetal health.

The first component of the program will be to join a NICHD-initiated FOA aimed at supporting the development and use of omics, alone or in conjunction with another technology. These grants should be geared toward developing omics profiles of human placental development from placental samples spanning at least 2 trimesters of an uncomplicated pregnancy, and ideally including samples taken at term. NIEHS would be receptive to projects that profile omic signatures in relation to environmental exposures to placental tissue, and may also include development of novel methods for real time sampling of placenta (cells, vesicles, RNA, proteins, etc.), or novel methods of performing non-invasive placental omics. We expect to continue to collaborate with NICHD on future placental research initiatives that fit within the scope of the ePOD program.

The second component of this program will be to develop funding opportunities to spur basic and epidemiological research to investigate placental exposures and to determine the life-long effects of chemical-induced placental damage during early pregnancy. Potential research gaps and needs addressed by the ePOD program include:

#### Human Studies

- Development of sensitive and non-invasive methods and biomarkers to assess early term exposures and their effects on placental and fetal health
- Improve and develop methods to assess exposures and placental function across gestation
- Determining time periods for greatest risk to placental health and their relationship to fetal and maternal health

#### Mechanistic Studies

- Development of better in vitro and in vivo models and methods to assess effects of placental exposures
- Determine which chemicals can alter placental structure and function
- Use of predictive tools and technologies to identify biomarkers of placental exposures and toxicity

These goals will be pursued through R21 and R01 grant mechanisms.