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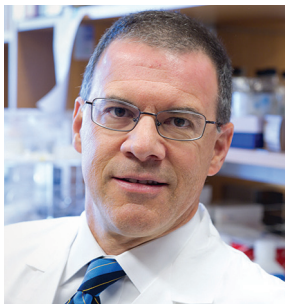
prematurity research center
The University of Pennsylvania

# In Pursuit of the Causes of Preterm Birth: Placental Dysfunction

The placenta plays a central role in nurturing a fetus through pregnancy, which is why researchers have long suspected its dysfunction could be a leading cause of preterm birth. In fact, placental dysfunction has been directly linked to other poor pregnancy outcomes such as miscarriage, stillbirth and preeclampsia.

Placental dysfunction has been defined as "failed invasion by placental trophoblast cells into the maternal uterine blood vessels." While we typically consider invasion negatively, trophoblast cell invasion is essential to support the fetus. The cells attack the small maternal blood vessels (with low blood flow) leading to the uterus, break down the vessel linings, and transform them into high flow, low resistance vessels. The result: ample blood flow into the placenta, enabling it to become the oxygen- and nutrient-rich organ that accomplishes so much:

- Floods the woman's body with essential hormones (progesterone and estrogen) to help the baby grow and develop
- Enables rich and plentiful oxygen flow and nutrient exchange from the mother to the baby
- Facilitates baby waste product transfer to the mother's blood stream for elimination



Samuel Parry, M.D.
*Associate Professor of Obstetrics and Gynecology, Chief of the Division of Maternal-Fetal Medicine at the University of Pennsylvania*

## Why the Failure to Invade?

Why do the trophoblast cells fail to invade? Secondly, does this contribute to preterm birth and, if so, what is the mechanism by which it causes preterm birth? Researchers in Theme Three, led by Samuel Parry, M.D., Associate Professor of Obstetrics and Gynecology, Chief of the Division of Maternal-Fetal Medicine at the University of Pennsylvania will attempt to answer this elusive question.

## Plan of Action

Theme Three researchers will work with doctors at the Hospital of the University of Pennsylvania, where 4,200 babies are delivered annually. Almost 12% of these babies are delivered too early due to spontaneous preterm labor. Researchers will take tissues and cells from placentas of women who deliver at term and preterm and study the metabolic functions of the placental tissue — mitochondrial function (energy), cell respiration, metabolites, among others — to see if different patterns emerge which explain why some women deliver preterm.

*continued*

Premature birth is one of the most intractable health challenges in modern medicine:

- One in nine babies in the United States is born prematurely each year
- Premature birth is the leading cause of newborn death in children from birth to age five
- Nearly half a million babies are affected annually
- Premature birth costs society at least $26 billion a year, according to the Institute of Medicine
- 15 million children are born prematurely every year worldwide
- Premature birth often leads to a lifetime of significant health challenges

The consequences of preterm birth extend to the entire family in terms of healthcare costs and impaired quality of life for the parents and siblings.

The March of Dimes Prematurity Research Center at The University of Pennsylvania is a robust, integrated cross-institutional effort. Its goal is to develop fundamental new insights into the biology of human pregnancy and the disease mechanisms of preterm birth to decrease the rate of prematurity and its associated complications. The March of Dimes intends to invest $75 million over five years to support the National Campaign to End Premature Birth.

To accomplish its goal, the March of Dimes Prematurity Research Center at the University of Pennsylvania has developed three interrelated theme areas, each bringing together renowned thinkers, researchers, physicians and top academics to focus on key aspects of the underlying causes of preterm birth.

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Once metabolic abnormalities are detected, Theme Three investigators will work with other researchers to study placental metabolism in the preterm animal models developed by Dr. Michal Elovitz, project leader for Theme Two. They will also work with Dongeun Huh, Ph.D., Assistant Professor of Bio-engineering, School of Engineering and Applied Science at Penn, who is developing a "placenta on a chip." This chip will place trophoblast cells on one side of a membrane and cells from fetal umbilical vessels on the other to emulate placental physiology and allow testing using real placental tissue identified as abnormal to see how it affects placenta function.

Some leading theories they will explore include:

1. **Mitochondrial (energy) function.** Mitochondria have been called the body's "cellular power plants." If testing shows that mitochondrial function is altered in preterm births, how might that impact placental physiology? If mitochondrial function is disturbed, perhaps trophoblast cells lack the cellular energy needed to successfully perform various placental functions that are essential to a normal pregnancy.
2. **Microbiome and Bacteria:** Are there unhealthy bacteria in the microbiome of preterm placental tissue? If so, how does a "high risk" microbiome alter trophoblast function? Does it cause inflammation that weakens the trophoblast cells?

These results will also be compared with those from Theme Two, which is looking at the impact of the microbiome on cervical remodeling. Theme Two's goals are to determine if unhealthy bacteria can lead to a dysbiotic state in the cervix, causing an exaggerated immune response and leading to abnormal cervical remodeling. Cervical remodeling is a key process in gestation that ultimately transforms cervical tissue from hard and inflexible into one that is soft and pliable to allow for a vaginal delivery.

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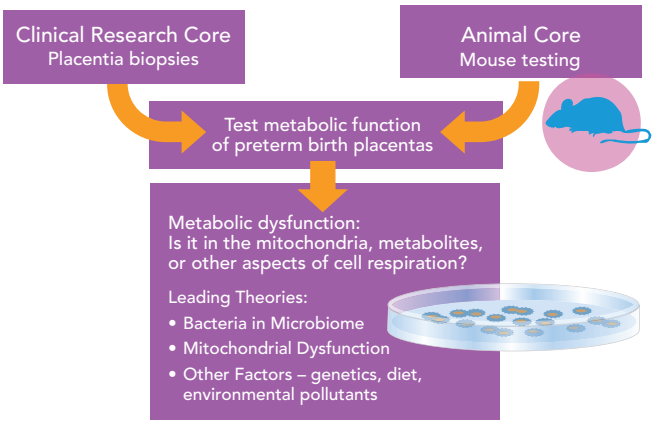


*Researchers will perform biopsies of placentas from women with preterm and term births to identify metabolic patterns that are disrupted in preterm births. Using mouse models and lab testing, researchers will try to identify potential causes — bacteria in the microbiome, mitochondrial deficiencies — and how this can impact trophoblast cell invasion that prepares the placenta to feed and nurture the fetus.*

"We hope this research will allow us to identify the metabolic processes in the placenta that go awry during preterm birth," adds Parry. "Ultimately, we will need to consider the factors that impact these metabolic processes, which can include genetics, diet, chemicals in food, stress and environmental pollutants and then take steps to reduce the incidence of preterm birth."

*For more information on how you can be a part of this effort, please contact*

David "D.J." Hampton II
*Senior Vice President & Chief Development Officer*
March of Dimes
1275 Mamaroneck Avenue
White Plains, NY 10605

Phone: 914.997.4492
philanthropy@marchofdimes.org

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