Placental Hypoxia-Inducible Factor 1 Alpha in Early-Onset Preeclampsia as a Predictor of Future Risk in Maternal and Fetal Health

Julie Slyby*, Bryce Linkous*, Sarah Scott*, Chandni Chandiramani*, Amy Hwang*, Danielle Spanbauer*, Melissa Kaufman*, Traci Rackett[v], Kailey Nolan[v], Emily Stone[v], Rose Maxwell[v], David Dhanraj[v], and Thomas L. Brown[*v]

*Department of Neuroscience, Cell Biology, and Physiology, [v]Department of Obstetrics and Gynecology

Boonshoft School of Medicine
WRIGHT STATE UNIVERSITY

Introduction

Preeclampsia is a life-threatening, pregnancy-associated disorder characterized by the rapid development of hypertension with renal dysfunction. While preeclampsia generally occurs later in pregnancy, early-onset preeclampsia (EOPE) can occur much earlier and is usually more devastating. Early-onset preeclampsia is also associated with an increased risk of maternal cardiovascular and metabolic disease in mothers later in life and neurocognitive dysfunction in their offspring. EOPE is strongly associated with abnormal placental development and fetal growth restriction during pregnancy.

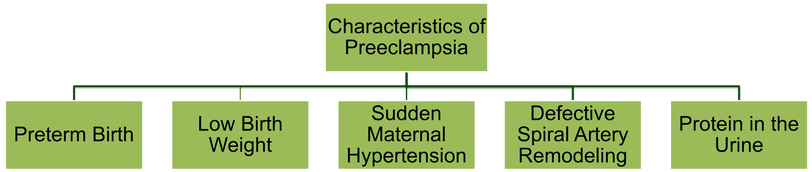

Figure 1. *The defining characteristics of preeclampsia, a pregnancy-associated disorder.*

The placenta is a transient organ that is formed during pregnancy and is essential for embryonic survival. Hypoxia-inducible factor 1 alpha (Hif-1α) is a critical oxygen-sensing transcription factor that has been implicated as a major regulator of trophoblast differentiation. Trophoblasts are cells that make up the fetal component of the placenta. Elevated Hif-1α has been linked to preeclampsia in humans. Our findings, in a newly developed mouse model, provide compelling evidence that Hif-1α is a critical molecular mediator of placental development and indicates that prolonged expression of Hif-1α, exclusively in placental trophoblasts during pregnancy, causes maternal pathology and fetal growth restriction that is characteristic of EOPE. Although the association of Hif-1α and preeclampsia has been suggested, no study has quantified the levels of Hif-1α in humans in EOPE pregnancies. In addition, a comparison between early- and late-onset preeclampsia has not been made. Our study will establish the relationship between Hif-1α-positive placentas and the risk of future preeclamptic pregnancies as well as future maternal health. This includes the prevalence of preeclampsia in a subsequent pregnancy, long-term maternal cardiovascular health, and health issues in the offspring including neurocognitive impairments. These findings will determine if Hif-1α is a predictive marker for the risk of future adverse effects from preeclampsia in both mothers and their offspring.

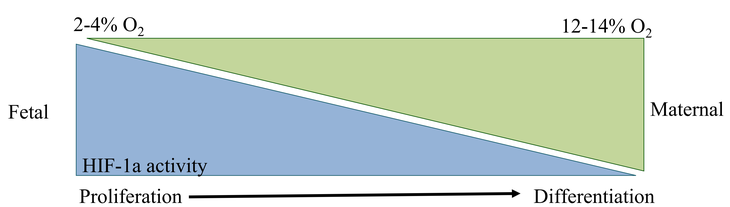

Figure 2. *Schematic of Hif-1α, hypoxia, and cell differentiation in the placenta.*

The Placenta

The placenta is a maternofetal organ that is essential to the survival of a developing fetus. The placenta is composed of maternal tissue derived from the endometrium and fetal tissue from the chorionic sac. Functions of the placenta include facilitating blood flow, gas and nutrient exchange, waste elimination, hormone production and regulating the body temperature of the fetus. The placenta is also an immunoprivileged organ—when exposed to antigens, there is no inflammatory response. Maternal blood and fetal blood do not come in contact through the placenta.

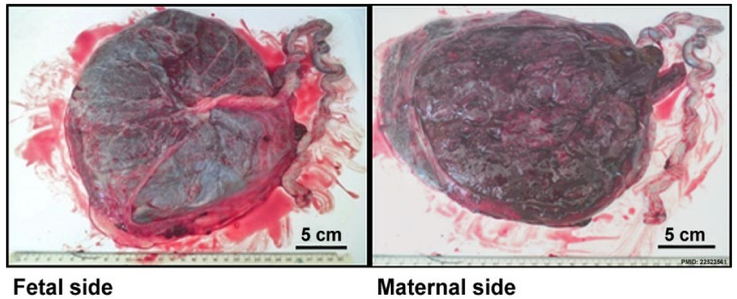

Figure 3. *Full term anatomical placenta.*

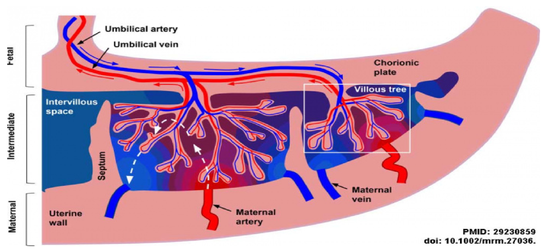

Figure 4. *Schematic of maternal and fetal arteries.*

Risk Factors for Preeclampsia

Antiphospholipid syndrome	Chronic kidney disease
Prior preeclamptic pregnancy	Advanced maternal age (>40)
Chronic hypertension	Family history of preeclampsia
Pregestational diabetes	First pregnancy
Multifetal pregnancy	Age
Obesity (BMI >30)	Systemic lupus erythematosus
In vitro fertilization (ART)	Prior pregnancy with IUGR

Procedure

Pregnant women at Miami Valley Hospital have been approached for participation in the study. Inclusion criteria include 1) age (18-40 years), 2) admission to labor and delivery, 3) diagnosis of preeclampsia, and 4) singleton pregnancy. Women who are obese or have diabetes have not been excluded but are noted to stratify the data.

Upon delivery, a member of the team collects the placenta directly from the delivery room and within 15 minutes collects tissue samples. 1 cm^3 of tissue is collected from four quadrants of each the fetal and maternal faces of the placenta.

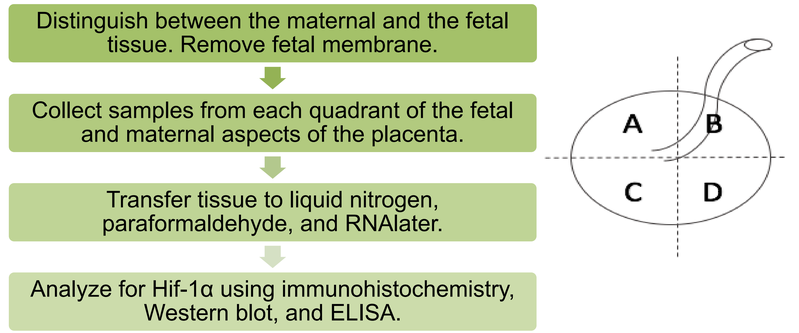

Figure 5. *Schematic of collection process and four-quadrant system, fetal aspect up.*

Expectations

This project will allow for us to determine the percentage of early onset preeclamptic pregnancies which are Hif-1α positive. This information will then be applied to the longitudinal portion of the study to allow for us to determine if Hif-1α can serve as a marker of preeclampsia in a subsequent pregnancy. In addition, other data such as preeclampsia with or without fetal growth restriction can be compared to the Hif-1α positive or negative placentas to determine other clinical findings that may be related to the presence of Hif-1α. We expect to answer are the following questions:

What is the prevalence of Hif-1α-positive EOPE pregnancies?

Is Hif-1α a predictive marker of EOPE in subsequent pregnancies?

Impact

If it is found that Hif-1α is a predictive marker of EOPE, women who are diagnosed with EOPE will could have their placentas tested for Hif-1α to determine the risk of EOPE in a subsequent pregnancy. In addition, this study will develop a longitudinal relationship between Hif-1α to subsequent pregnancies in the mother and their offspring.

Acknowledgements

This work was funded by NIH-R01 grant HD059969-(TLB) and the Endowment for Research on Pregnancy-Associated Disorders (www.wright.edu/give/pregnancyassociateddisorders).