**Introduction**

Preeclampsia (PE) is a multisystem vascular disorder originating in the placenta that is responsible for over 70,000 maternal deaths and 5 million STH annual worldwide. In Bolivia, a low to middle income country in Latin America, maternal and infant mortality rates are three times higher in the Western Hemisphere. This high rate is in part due to the fact that Bolivia’s population (~8 million) resides at high altitudes (~2,500 m) where incidence of PE, fetal growth restriction, and neonatal respiratory distress are three-fold greater than at low altitude. Despite the public health concern and increased funding to identify therapeutic targets and molecular markers, the etiology of placental remodeling remain elusive. There has been an increasing body of literature supporting the involvement of vascular dysfunction in PE patients. Insulin resistance has been found in placentas from PE, fetal growth restriction, and gestational diabetes pregnancies. Additionally, impaired insulin signaling has been reported to induce vascular dysfunction, perhaps contributing to the vascular dysfunction that is hallmarked of PE.

Normally, binding of insulin to the insulin receptor (IR) leads to its activation, yielding phosphorylation of the insulin receptor substrate (IRS) proteins. Activation of IRS creates a docking point for phosphatidylinositol-3 kinase (PI3K) and with its binding, leads to the activation of protein kinase B (AKT). Once activated, AKT phosphorylates proteins involved with glucose uptake and metabolism. For example, Akt inhibits Glycogen Synthase 1 (GYS1), leading to glycogen synthesis. However, in insulin resistance, activation of PI3K creates a decrease in Akt activity, leading to a reduction of glycogen synthesis, as well as decreased nitric oxide production, causing vasoconstriction.

For insufficient oxygen tension, or hypoxia, has been shown to affect the insulin signaling pathway and be involved in the pathology of PE. Hypoxia alters placental expression of markers of hypoxia in the syncytiotrophoblast receptor of Epo has been shown to be increased in high-altitude or PE pregnancy. Hypoxia has been shown to create a state of insulin resistance through hypoxia-inducible factors (HIF-1alpha) and could be implicated in the development of PE via insulin signaling dysfunction. The PI3K/Akt pathway has also been involved in hypoxia-ischemia alongside insulin resistance, suggesting a possible link between hypoxia, the Akt pathway and insulin resistance as a potential mechanism for the development of PE.

**Hypothesis**

The insulin signaling pathway is impaired in preeclamptic placenta versus controls, specifically the IRS/Akt pathway protein expression is altered in PE.

Placental protein expression involved with the insulin signaling pathway will be correlated with the hypoxia marker EpoR.

**Aims**

1. To establish whether placental insulin signaling was altered in PE case at high altitude.
2. To determine whether PI3K/Akt protein expression was enhanced in PE placenta, and to establish the relationship between protein expression and placental hypoxia.

**Methods**

 Patients were enrolled following review of medical records under IRB approval No. 19-0203 as well as the Bolivian equivalence. All patients were between the ages of 18-48 and were 20-38 weeks gestation. Pregnancies requiring cesarean or delivering a Hospital Materno-Infantil in La Paz, Bolivia were excluded for study. PE was defined using American College of Obstetricians and Gynecologists (ACOG) or small hypertension as described by Kofinas et al. All patients had both maternal or fetal outcomes, including maternal blood pressure, laboratory values, and pregnancy complications were obtained from medical records. Newborns and fetal complications, birth weight, gestational age at delivery, delivery method, birth weight, and gestational age at delivery.

At enrollment, information regarding maternal age, ethnicity, reproductive history, health history, history of placental complications, obstetric history, education level, and marital status was obtained from medical records or by questioning the patient (history of PE). Patients were within 15 minutes after delivery. No. Prenatal visit information, including maternal blood pressure, laboratory values, and pregnancy complications were obtained from medical records. Newborns and fetal complications, birth weight, gestational age at delivery, birth weight, gestational age, and age were measured from hospital records.

Placental biopsies were obtained and processed per established protocols. Placental samples were processed within 30 minutes of delivery. Protein was extracted from each placental tissue with a mixture of protein concentrations determined by sodium dodecyl sulfate (SDS) analysis (Thermo Fisher Scientific) using 1.3 mg/mL of each sample. Placental samples were then calculated to a 1 mg/mL solution concentration in 0.1% sample buffer (Proteinase K, Thermo Fisher Scientific). Data were analyzed using Compass software (Pall)."