Worldwide, 15 million infants are born too soon each year and more than one million of those infants die as a result of their early births. The frequency of spontaneous preterm deliveries (sPDT) is increasing in emergent and developing countries and it represents a major public health issue with about 11.7% prevalence in the USA in 2011 and ranging between 5-15% in many other countries.\(^1\)\(^2\) Data regarding nocturnal versus diurnal circadian patterns of sPDT onset are conflicting. Additionally, little has been done to assess the extent to which, if at all, there are differences in the circadian patterning of the onset of spontaneous preterm labor (sPTL) and preterm premature rupture of membranes (PPROM), respectively.\(^3\)\(^4\) Increased understanding of circadian rhythms in pregnancy and parturition may yield important insights into the pathophysiological processes underlying the mechanisms of preterm births and this could aid in the development of novel treatments and sPDT prevention strategies.

The generation of circadian rhythms is based on rhythmic expression of clock genes.\(^5\) The recent recognition that clock genes are expressed in the placenta, together with observations linking circadian disruption with compromised placental function, suggests that circadian variation may be an important component of sPDT pathophysiology.

**a) Research Strategy:** Recently, I have been using advanced statistical approaches under the theoretical framework of chronobiology to characterize the circadian variation in sPTL and PPROM onset among 476 women who delivered a singleton live-birth between 2009 and 2010 in Lima, Peru. I used parametric and nonparametric methods (Epanechnikov kernel function) and Fourier analysis to describe the data, and trigonometric models and piecewise cubic spline regressions to model the time of the onset of sPDT.\(^6\)\(^7\)\(^8\)\(^9\) These statistical methods had never been applied to studies of preterm birth. I found that the time of onset of sPDT was characterized by a predominant diurnal circadian pattern, which was similar for deliveries preceded by either sPTL or PPROM. I then sought opportunities to repeat my analyses in an independent data set. Hence, I developed a collaboration with Professor C. Ananth at Columbia University. As a result of this collaboration, I was able to apply the same statistical analytical methods to a much larger study population of subjects enrolled in the National Collaborative Perinatal Project (NCPP), a large (N=53,391) independent sample of women delivering in the US between 1959 and 1966. I was able to document the same diurnal circadian pattern for preterm and term deliveries\(^10\). My preliminary results suggest that circadian rhythms may also modulate physiologic processes underlying the timing of sPDT. *Hence, going forward the principal aim of my research program is to replicate my analysis with high quality data from the nationwide Medical Birth Registry in Iceland. And secondly to explore possibilities for integrating genome wide association studies (GWAS) and candidate gene analytical approaches for studying the potential role of “clock” genes in placental physiology and sPDT.*

**b) Travel plans and collaborators:** During a recent research meeting, I had the opportunity to present my preliminary results to Dr. Unnur Valdimarsdottir, Professor in the Center of Public Health Sciences, University of Iceland; and Adjunct Professor of Epidemiology, HSPH. Dr. Valdimarsdottir suggested that I work to establish a cross-institutional collaborative relationship that will allow me access to Icelandic vital registration data to identify over 2,500 sPDT cases among 50,000 term deliveries over a period of ten years. In addition to replicating my preliminary findings, I want to develop a case control study to explore sPDT risk associated with variants in “clock” genes. Thus, I would like to use the Røste Travel Fellowship to travel to Reykjavik, Iceland in April 2014 and spend 1-2 months in field work to organize medical records abstraction for time of onset of delivery and to merge that data into the Medical Birth Register. I will also explore ways to perform data linkage between the MBR and the database at deCode Genetics to obtain maternal genotypes.

**c) Background and skills:** I am a postdoctoral fellow in Epidemiology (Mentor: Dr. Williams) with a multidisciplinary academic background. I completed my PhD in Epidemiology at the University of Granada, Spain and Brussels, Belgium in 2010. I have research experience in the fields of maternal and perinatal health. Together with Dr. Valdimarsdottir, I have already established a preliminary agenda of activities to develop during my visit. First, Dr. Valdimarsdottir has encouraged me to acquire the computing and software skills needed to the use of the Icelandic vital statistics data and the medical electronic register. In addition, I will have to apply deterministic linkage methods with the open source software FLIR\(^1\) to obtain other relevant personal medical information, such as genotypes from the IHD\(^12\). Second, I will train a research nurse to abstract medical records information relevant to the modeling of the time of onset of sPDT and spontaneous term labor among a random sample of births to singleton mothers in the past decade. I will be responsible for developing the abstraction form, completing quality assessments of collected data, linkage strategies and completing statistical analyses, and preparing a first draft of the study report.

**d) Overall academic and career goals:** The replication of my analyses using identical methods in different data sets that records the experiences of women of diverse racial, ethnic and geographic backgrounds, will help to confirm my preliminary findings and expand the generalizability of my observation that circadian rhythms are evident in the timing of sPDT. *Results from these multiracial/multiethic analyses will be summarized in peer-reviewed research publications.* The support from the Rose Travel Fellowship will help me to achieve my long term academic and career goal of becoming an independent investigator. This opportunity will enlarge my international cultural experience, and I will gain experience in developing a collaborative research partnership with faculty in Iceland. In addition, this fellowship will allow me an opportunity to generate a platform of future research that may be used in future NIH research grant proposals (e.g., K-award and R-21). This collaborative partnership will also offered me the unique opportunity to meet with geneticists and assess the feasibility of conducting GWAS and candidate gene analytical approaches to explore others physiological rhythms entrained by circadian “clock” genes implicated in placental physiology and a range of pathologies including cancer, obesity and diabetes.\(^13\)\(^14\)
References


